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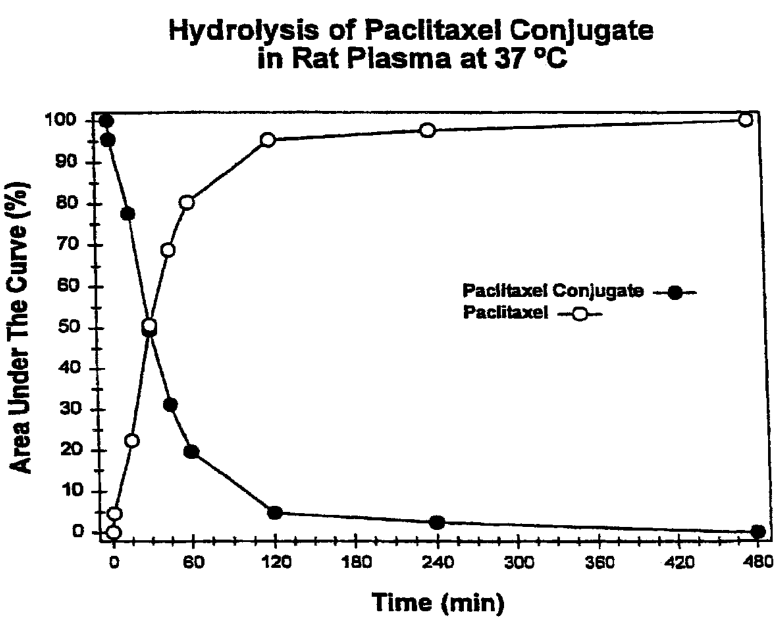
(54) Title: TAXANE PRODRUGS



(57) **Abstract:** The present invention generally provides taxane prodrugs comprising at least one taxane joined by hydrolyzable bond(s) to one or more polyethylene glycol oligomer(s) selected from the group consisting of a straight or branched polyethylene glycol oligomer having from 1 to 25 polyethylene glycol units and optionally comprising a salt-forming moiety. The polyethylene glycol oligomer preferably comprises a salt-forming moiety, which is preferably selected from the group consisting of ammonium and carboxylate.

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TAXANE PRODRUGS

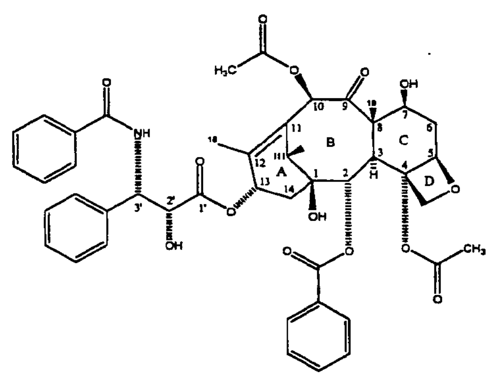
1. Background of the Invention

1.1 Field of the Invention

The present invention relates generally to taxane-oligomer conjugates and to methods for making and using such conjugates. The taxane-oligomer conjugates of the invention operate as prodrugs, hydrolyzing under normal physiological conditions to provide therapeutically active taxanes, such as paclitaxel or docetaxel. The taxane-oligomer conjugates exhibit improved solubility characteristics, improved oral bioavailability, and an improved pharmacokinetic profile. The present invention also relates to pharmaceutical compositions comprising these taxane-oligomer conjugates and to methods of making and using such taxane-oligomer conjugates and pharmaceutical compositions.

1.2 Description of the Prior Art

Paclitaxel (Taxol) is a natural diterpene product isolated from the pacific yew tree (*Taxus brevifolia*). Wani et al. first isolated paclitaxel in 1971 by chemical and X-ray crystallographic methods. Paclitaxel is a complex diterpene having a taxane ring with a 4-membered oxetane ring and an ester side chain at position C-13. The complex structure of paclitaxel is as follows:



(Formula 1)

Paclitaxel has been approved for clinical use in the treatment of refractory ovarian cancer in the United States. (Markman 1991; McGuire et al. 1989). Paclitaxel has also been approved for treatment of breast cancer. (Holmes et al. 1991) Additionally, paclitaxel is a candidate for treatment of neoplasms of the skin (Einzig et al.) and head and neck carcinomas (Forastire et al.

1990). Paclitaxel is also useful for the treatment of polycystic kidney disease (Woo et al. 1994), lung cancer and malaria.

Paclitaxel mediates its anti-cancer effects by lowering the critical concentration of tubulin necessary for microtubule formation. Microtubules are polymers of tubulin in dynamic equilibrium with tubulin heterodimers that are composed of α and β protein subunits. Paclitaxel shifts the equilibrium towards microtubule assembly. Paclitaxel-induced microtubules are excessively stable, thereby inhibiting dynamic reorganization of the microtubule network, and resulting in microtubule bundles that form during all phases of the cell cycle and numerous abnormal mitotic asters that are not associated with centrioles.

Paclitaxel entered Phase I clinical trials in 1983, but immediately encountered formulation difficulties due to its aqueous insolubility. This difficulty was partially overcome by formulating Paclitaxel as an emulsion with Cremophor EL®. However, since paclitaxel must be given at relatively high dosages, large amounts of Cremophor EL® are required. When administered intravenously, such formulations can produce vasodilatation, labored breathing, lethargy, hypertension and death in dogs, and are also believed to be responsible for the allergic-type reactions observed during paclitaxel administration in humans. Accordingly, there is a need in the art for a means for administering paclitaxel which increases its water solubility and thereby avoids the need for formulating paclitaxel with potentially allergenic emulsion reagents.

Efforts to overcome the allergy problems of formulated paclitaxel have thus far been directed at lengthening the infusion time and premedicating patents with immunosuppressive agents, such as glucocorticoids and also with antihistamines. These agents have their own set of side effects and are an added cost to the already expensive cost of cancer treatment. Furthermore, while such agents have been shown to reduce the incidence and severity of hypersensitivity reactions, they are not fully protective. (Rowinsky et al. 1992). Accordingly, there is a need in the art for means for administering paclitaxel which avoids lengthened infusion times and the allergic reactions associated with emulsion reagents and thereby also avoids the need for such adjunctive treatment.

Several groups have investigated the synthesis of prodrug forms of paclitaxel. (Taylor 1994); (Kingston, D.G. 1991). Prodrugs are inactive or partially inactive chemical derivatives of drugs that are metabolized to yield the pharmacologically active drug. Studies have been directed toward synthesizing paclitaxel analogs where the 2' and/or 7-position is derivatized with groups that enhance water solubility. These efforts have yielded prodrug compounds that are more water-

soluble than the parent compound while displaying the cytotoxic properties of paclitaxel upon activation. For example, increased water-solubility has been achieved by derivatizing paclitaxel with high molecular weight polyethylene glycol (PEG) polymers. (See Greenwald, et al. 1996; Greenwald et al. 1995). However, while these derivativized paclitaxel compounds have increased solubility, they also result in a corresponding decrease in drug load, due to the high molecular weight PEG necessary to achieve adequate solubility. Accordingly, there is a need in the art for taxane prodrugs which improve paclitaxel solubility without drastically increasing the molecular weight of the paclitaxel compound.

Efficient utilization of prodrugs, especially taxane prodrugs, requires that the properties of the prodrug must be adequately balanced to achieve a useful pharmacokinetic profile. In one aspect, it is desirable for the prodrug to be hydrophilic in order to enhance the ability to formulate the prodrug. On the other hand, the prodrug must be appropriately hydrophobic to permit interaction of the prodrug with biological membranes. There is therefore a need in the art for taxane prodrugs that accommodate the foregoing disparate requirements for useful therapeutic agents.

2. Summary of the Invention

The present inventors have surprisingly and unexpectedly discovered taxane-oligomer compounds and salts of such compounds (collectively referred to herein as "taxane prodrugs") that significantly increase the water-solubility of taxane drugs without drastically increasing their molecular weight. The taxane prodrugs described herein eliminate the need for microemulsion formulation using Cremophor EL®.

The present invention generally provides taxane prodrugs comprising at least one taxane joined by hydrolyzable bond(s) to one or more polyethylene glycol (PEG) oligomers. The PEG oligomers consist of a straight or branched polyethylene glycol oligomer having from 1 to 25 polyethylene glycol units and optionally comprise a salt-forming moiety. Preferably, the PEG oligomer comprises a salt-forming moiety, such as ammonium or carboxylate.

In a preferred aspect of the present invention, the taxane portion of the taxane prodrug is paclitaxel or a paclitaxel analog which retains some or all of the therapeutic activity of paclitaxel. Another preferred taxane is docetaxel.

The taxane prodrug may be derivatized by as many PEG oligomers as there are sites on the taxane for attachment of such oligomers. For example, paclitaxel has 3 attachment sites (hydroxyl groups)

and can therefore be derivatized by 1, 2 or 3 of the oligomers. Similarly, docetaxel paclitaxel has 4 attachment sites (hydroxyl groups) and can therefore be derivatized by 1, 2, 3 or 4 of the oligomers.

In another aspect, the taxane prodrugs can be delivered via oral administration to provide a therapeutically effective dose of the taxane to the bloodstream. Furthermore, the orally delivered derivatives can provide a therapeutically effective dose of the taxane to the target organ or tissue.

The present invention also provides pharmaceutical compositions comprising the taxane prodrugs of the invention in association with a pharmaceutically acceptable carrier. Such pharmaceutical compositions may be formulated so as to be suitable for oral administration, and may be in a dosage form selected from the group consisting of: tablets, capsules, caplets, gelcaps, pills, liquid solutions, suspensions or elixirs, powders, lozenges, micronized particles and osmotic delivery systems.

In another aspect, the present invention provides a taxane prodrug comprising a taxane joined by hydrolyzable bond(s) to one or more polyethylene glycol oligomer(s) selected from the group consisting of:

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{R}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 2)}$$

wherein n is from 1 to 7, m is from 2 to 25, and R is a lower alkyl preferably selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl and *t*-butyl;

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2)_p-\overset{R}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 3)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, and R is a lower alkyl, preferably selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl and *t*-butyl;

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-CH_2CH_2(OC_2H_4)_r-\overset{R}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 4)}$$

wherein n is from 1 to 6, m and r are each independently from 2 to 25, and R is a lower alkyl, preferably selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl and *t*-butyl;

$$-\overset{\overset{\Large O}{\|}}{C}-(CH_2)_n-\overset{\overset{\Large O}{\|}}{C}-\overset{H}{N}-(CH_2)_p-\overset{\overset{R}{|}}{N}-CH_2CH_2(OC_2H_4)_mNH_2 \quad \text{(Formula 5)}$$

wherein n is from 1 to 6, p is from 2 to 8 and m is from 2 to 25 and R is a lower alkyl, preferably selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl and *t*-butyl ;

$$-\overset{\overset{\Large O}{\|}}{C}-(CH_2)_n-\overset{\overset{\Large O}{\|}}{C}-\overset{H}{N}-(CH_2)_p-\overset{\overset{R}{|}}{N}-CH_2CH_2(OC_2H_4)_mNH_3^+X^- \quad \text{(Formula 6)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, X^- is a negative ion, preferably selected from the group consisting of chloro, bromo, iodo, phosphate, acetate, carbonate, sulfate, tosylate and mesylate, and R is a lower alkyl, preferably selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl and *t*-butyl ;

$$-\overset{\overset{\Large O}{\|}}{C}-(CH_2)_n-\overset{\overset{\Large O}{\|}}{C}-\overset{H}{N}-(CH_2)_p-\overset{\overset{R^1}{|}}{N}-CH_2CH_2(OC_2H_4)_mNHR^2 \quad \text{(Formula 7)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, and R^1 and R^2 are each independently a lower alkyl, preferably selected from the group consisting of methyl, ethyl, propyl, isopropyl, and *t*-butyl;

$$-\overset{\overset{\Large O}{\|}}{C}-(CH_2)_n-\overset{\overset{\Large O}{\|}}{C}-\overset{H}{N}-CH_2CH_2(OC_2H_4)_mOCH_2-\overset{\overset{\Large O}{\|}}{C}-NH(CH_2)_pN(CH_3)_2 \quad \text{(Formula 8)}$$

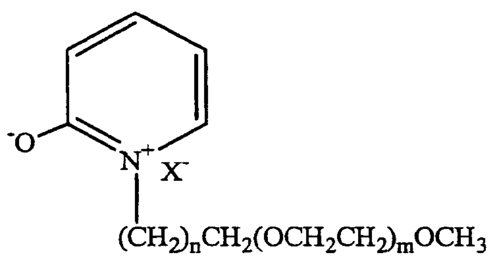
wherein n is from 1 to 6, p is from 2 to 8 and m is from 2 to 25;

$$-\overset{\overset{\Large O}{\|}}{C}-(CH_2)_n(OC_2H_4)_mO(CH_2)_p-\overset{\overset{\Large O}{\|}}{C}-O^-X^+ \quad \text{(Formula 9)}$$

wherein n and p are each independently from 1 to 6, m is from 2 to 25 and X^+ is a positive ion, preferably selected from the group consisting of hydrogen, sodium, potassium, calcium, lithium and ammonium salts;

$$-\overset{\displaystyle O}{\overset{\|}{C}}-(CH_2)_n-\underset{\displaystyle R^2}{\underset{|}{\overset{\displaystyle R^1}{\overset{|}{N}}}}-CH_2CH_2(OC_2H_4)_mOCH_3 \quad \text{(Formula 10)}$$

wherein n is from 1 to 5, m is from 2 to 25, and wherein R^1 and R^2 are each independently lower alkyl and are preferably independently selected from the group consisting of hydrogen, methyl, ethyl propyl, isopropyl and *t*-butyl; and



(Formula 11)

wherein n is from 1 to 6, m is from 2 to 25 and X^- is a negative ion, preferably selected from the group consisting of: chloro, bromo, iodo, phosphate, acetate, carbonate, sulfate, and mesylate.

Any of the foregoing oligomers of Formulae 2-11 may suitably comprise a salt-forming moiety. Preferred salt-forming moieties are ammonium, hydrogen, sodium, potassium, lithium, calcium, carboxylate, chloride, bromide, iodide, phosphate, sulfate and mesylate.

The preferred taxane components of the taxane prodrugs are paclitaxel and docetaxel. The taxane may also be another paclitaxel analog which retains some or all of the therapeutic activity of paclitaxel, or exhibits improved activity as compared to paclitaxel. The taxane is derivatized by a number of PEG oligomers which does not exceed the number of sites of attachment for such oligomers. Thus where the taxane component of the taxane prodrug is paclitaxel or docetaxel, it can be derivatized by 1, 2 or 3 of the PEG oligomers of Formulae 2-11.

The present invention also provides pharmaceutical compositions comprising a taxane prodrug of Formulae 2-11 and a pharmaceutically acceptable carrier. The pharmaceutical composition can be formulated to be suitable for oral administration, and can be in any of a variety of pharmaceutical dosage forms, such as tablets, capsules, caplets, gelcaps, pills, liquid solutions, suspensions or elixirs, powders, lozenges, micronized particles and osmotic delivery systems.

The present invention also provides a method for treating a mammalian subject having a paclitaxel-responsive disease condition, said method comprising administering to the subject a therapeutically

effective amount of a taxane prodrug comprising a taxane joined by hydrolyzable bond(s) to one or more polyethylene glycol oligomers selected from the group consisting of a straight or branched polyethylene glycol oligomer having from 2 to 25 polyethylene glycol units and optionally comprising a salt-forming moiety and /or its corresponding salt.

The present invention also provides a method for treating a mammalian subject having a taxane-responsive disease condition, such as a paclitaxel-responsive or docetaxel-responsive condition, said method comprising administering to the subject a therapeutic amount of a taxane derivativized by any of the Formulae 1-11. The mammalian subject is preferably a human.

In one aspect of the methods of treatment, the taxane prodrug is delivered via an oral route of administration to provide a therapeutically effective dose of the taxane into the bloodstream. In another aspect, the taxane prodrug is delivered via a parenteral route of administration, providing a therapeutically effective dose of the taxane to target organs and/or tissues. In yet another aspect, the taxane prodrug is delivered via an oral route of administration, providing a therapeutically effective dose of the taxane to target organs and/or tissues. Furthermore, the taxane prodrug may be administered in association with a pharmaceutically acceptable carrier.

In a further aspect, the taxane-responsive disease condition treated according to the therapeutic methods of the invention is selected from the group consisting of benign and malignant neoplasms, and may include hepatocellular carcinoma, urogenital carcinoma, liver metastases, gastrointestinal cancers, lymphoma, leukemia, melanoma, Kaposi's sarcoma, and cancers of the pancreas, kidney, cervix, breast, ovary, brain, and prostate. In one aspect, the disease condition comprises ovarian cancer and the taxane prodrug is administered optionally with cisplatin, either simultaneously or sequentially. In another aspect, the disease condition comprises breast cancer and the taxane prodrug is administered optionally with doxorubicin, either simultaneously or sequentially.

2.1 Definitions

As used herein the term "PEG" refers to straight or branched polyethylene glycol oligomer and monomers and also includes polyethylene glycol oligomers that have been modified to include groups which do not eliminate the amphiphilic properties of such oligomer, e.g. without limitation, alkyl, lower alkyl, aryl, amino-alkyl and amino-aryl. The term "PEG subunit" refers to a single polyethylene glycol unit, i.e., $-(CH_2CH_2O)-$.

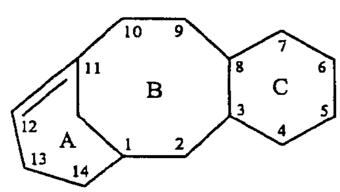
As used herein, the term "lower alkyl" refers to a straight or branched chain hydrocarbon having from one to 8 carbon atoms.

As used herein, terms such as "non-hydrolyzable" and phrases such as "not hydrolyzable" are used to refer to bonds which cannot be hydrolyzed under normal physiological conditions, as well as bonds which are not rapidly hydrolyzed under normal physiological conditions such as carbamate and amide bonds. The term "hydrolyzable" refers to bonds which are hydrolyzed under physiological conditions. In a preferred aspect of the invention, 50% of the taxane prodrug is hydrolyzed in a normal population within 4 hours after intravenous administration.

A "therapeutically effective amount" is an amount necessary to prevent, delay or reduce the severity of the onset of disease, or an amount necessary to arrest or reduce the severity of an ongoing disease, and also includes an amount necessary to enhance normal physiological functioning.

As used herein, a "pharmaceutically acceptable" component (such as a salt, carrier, excipient or diluent) of a formulation according to the present invention is a component which (1) is compatible with the other ingredients of the formulation in that it can be combined with the taxane prodrugs of the present invention without eliminating the biological activity of the taxane prodrugs; and (2) is suitable for use with an animal (e.g., a human) without undue adverse side effects, such as toxicity, irritation, and allergic response. Side effects are "undue" when their risk outweighs the benefit provided by the pharmaceutical composition. Examples of pharmaceutically acceptable components include, without limitation, standard pharmaceutical carriers, such as phosphate buffered saline solutions, water, emulsions such as oil/water emulsions, microemulsions, and various types of wetting agents.

As used herein, the term "taxane" is used to refer to a class of compounds having a basic three ring structure which includes rings A, B and C of paclitaxel:



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including, without limitation, paclitaxel and paclitaxel analogs which retain some or all of the anti-cancer activity of paclitaxel.

3. Brief Description of the Drawings

Figure 1 shows the conversion of acetate (Compound 4) (see Examples below) to paclitaxel over the course of 26 days at room temperature, where the acetate (Compound 4) was dissolved in wet acetonitrile. Figure 1 shows that acetate (Compound 4) smoothly converted quantitatively into paclitaxel with no significant side product formation, as observed by analytical HPLC analysis.

Figure 2 shows *in vitro* hydrolysis of acetate (Compound 4) in heparinized rat plasma and demonstrates that most of the taxane prodrug rapidly hydrolyzes within two hours to provide free paclitaxel.

4. Detailed Description of the Invention

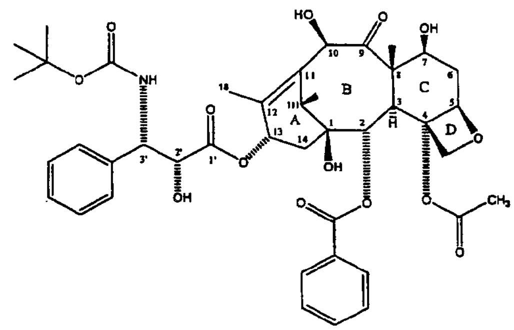
The ensuing detailed description is divided into sections for ease of reference only. Subject headings are not intended to limit the scope of the invention.

4.1 Taxane-Oligomer Prodrugs

The present invention provides taxane-oligomer prodrugs (also referred to herein as "taxane prodrugs"). The taxane prodrugs of the present invention generally comprise a taxane component and a PEG oligomer component. The taxane prodrugs are generally useful in facilitating the formulation of taxanes in a hydrophilic formulation, the oral delivery of taxanes, and the delivery of taxanes to target organs and tissues.

4.1.1 Taxanes

Preferred taxanes are those having the constituents known in the art to be required for enhancement of microtubule formation, e.g., paclitaxel and docetaxel. The structures of paclitaxel and docetaxel are known in the art; however, for ease of reference, the structural formula of paclitaxel is set forth in Figure in Section 1.2 above, and the structural formula for docetaxel is as follows:



In a preferred mode, the taxane of the taxane prodrug is a paclitaxel analog. Many analogs of paclitaxel are known in the art which display more or less anti-cancer activity than paclitaxel itself. The present invention contemplates the use of any paclitaxel analog that does not have completely diminished anti-cancer activity.

In one class of analogs, the side chain *N*-benzoyl group is replaced with other acyl groups. One such analog, docetaxel (Taxotere®), has an *N-t*-butoxycarbonyl group in place of the *N*-benzoyl group of paclitaxel and also lacks the 10-acetate group. Docetaxel is known to be about five times as active as paclitaxel against paclitaxel-resistant cells and is currently in clinical use in both France and the U.S.A.

It is also known that reduction of the C-9 carbonyl group to an α-OH group causes a slight increase in tubulin-assembly activity. Additionally, it is known that a rearrangement product with a cyclopropane ring bridging the seven and eight-position is almost as cytotoxic as paclitaxel.

Further suitable taxanes for use in the taxane prodrugs of the present invention are paclitaxel derivatives having structural variations along the "northern perimeter" portion of the paclitaxel molecule. The "northern perimeter" comprises carbons 6-12, with oxygen functions at C-7, C-9 and C-10. Many such derivatives are known in the art, and it is known that such derivatives exhibit biological activity that is comparable to the bioactivity of paclitaxel. Thus, for example, it is known acylation of the C-7 hydroxyl group, or its replacement with hydrogen, does not significantly reduce the activity of paclitaxel. Additionally, replacement of the 10-acetoxy group with hydrogen causes only a small reduction in activity.

It has been noted that *m*-substituted benzoyl derivatives are more active than their *p*-substituted analogs, and are often more active than paclitaxel itself.

Another paclitaxel analog suitable for use in the taxane prodrugs of the present invention is A-nor-paclitaxel. This analog has tubulin-assembly activity that is only three times less than that of paclitaxel. A-nor-paclitaxel and paclitaxel have very similar molecular shapes, which may explain their similar tubulin-assembly activities.

4.1.2 Polymers/Oligomers

The PEG polymers/oligomers of the taxane prodrugs of the present invention may be straight or branched. Preferred oligomers have from 2 to 25 PEG units, more preferably from 2 to 20 PEG units, still more preferably from 2 to 15 PEG units. Ideally, the PEG oligomer has from 2 to 10 PEG units, i.e., 2, 3, 4, 5, 6, 7, 8, 9 or 10 PEG units. In another aspect, the PEG oligomer has a molecular weight which is not greater than 1000.

In a preferred mode, the PEG polymers/oligomers have the formula:

$$-(CH_2CH_2O)_X-CH_3 \qquad \text{(Formula 1)}$$

wherein X = 2-25.

In a more preferred mode, X is from 2-20, still more preferably from 2-15, and most preferably from 2-10. Ideally, X is 2, 3 , 4 , 5, 6, 7, 8, 9 or 10.

Preferred PEG oligomers are selected from the group consisting of:

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n-\overset{\overset{\displaystyle R}{|}}{N}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 2)}$$

wherein n is from 1 to 7, m is from 2 to 25, and R is a lower alkyl preferably selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl and *t*-butyl;

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{H}{N}-(CH_2)_p-\overset{\overset{\displaystyle R}{|}}{N}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 3)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, and R is a lower alkyl, preferably selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl and *t*-butyl;

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-CH_2CH_2(OC_2H_4)_r-\overset{R}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 4)}$$

wherein n is from 1 to 6, m and r are each independently from 2 to 25, and R is a lower alkyl, preferably selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl and *t*-butyl;

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2)_p-\overset{R}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mNH_2 \qquad \text{(Formula 5)}$$

wherein n is from 1 to 6, p is from 2 to 8 and m is from 2 to 25 and R is a lower alkyl, preferably selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl and *t*-butyl ;

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2)_p-\overset{R}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mNH_3^+X^- \qquad \text{(Formula 6)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, X^- is a negative ion, preferably selected from the group consisting of chloro, bromo, iodo, phosphate, acetate, carbonate, sulfate, tosylate and mesylate, and R is a lower alkyl, preferably selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl and *t*-butyl ;

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2)_p-\overset{R^1}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mNHR^2 \qquad \text{(Formula 7)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, and R^1 and R^2 are each independently a lower alkyl, preferably selected from the group consisting of methyl, ethyl, propyl, isopropyl, and *t*-butyl;

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-CH_2CH_2(OC_2H_4)_mOCH_2-\overset{O}{\overset{\|}{C}}-NH(CH_2)_pN(CH_3)_2 \qquad \text{(Formula 8)}$$

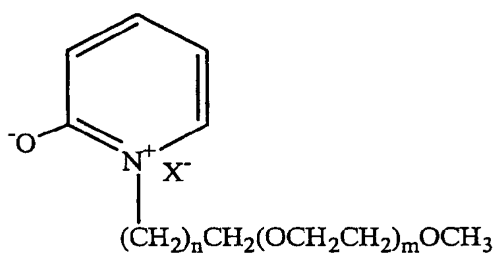
wherein n is from 1 to 6, p is from 2 to 8 and m is from 2 to 25;

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n(OC_2H_4)_mO(CH_2)_p-\overset{O}{\overset{\|}{C}}-O^-X^+ \qquad \text{(Formula 9)}$$

wherein n and p are each independently from 1 to 6, m is from 2 to 25 and X^+ is a positive ion, preferably selected from the group consisting of hydrogen, sodium, potassium, calcium, lithium and ammonium salts;

$$-\overset{\overset{\large O}{\|}}{C}-(CH_2)_n-\underset{\underset{\large R^2}{|}}{\overset{\overset{\large R^1}{|}}{N}}-CH_2CH_2(OC_2H_4)_mOCH_3 \quad \text{(Formula 10)}$$

wherein n is from 1 to 5, m is from 2 to 25, and wherein R^1 and R^2 are each independently lower alkyl and are preferably independently selected from the group consisting of hydrogen, methyl, ethyl propyl, isopropyl and *t*-butyl; and



(Formula 11)

wherein n is from 1 to 6, m is from 2 to 25 and X^- is a negative ion, preferably selected from the group consisting of chloro, bromo, iodo, phosphate, acetate, carbonate, sulfate, tosylate and mesylate.

In any of the foregoing Formulae 1-11, the total number of PEG units is preferably from 2 to 25, more preferably from 2-20, still more preferably from 2-15, most preferably from 2-10. Ideally, the total number of PEG units is 2, 3 , 4 , 5, 6, 7, 8, 9 or 10. In formulae, such as Formula 4, which contain two PEG polymer segments, the preferred number of PEG units set forth in this paragraph may be contained completely in either of the two PEG polymer segments or may be distributed between the two PEG polymer segments.

The PEG-oligomer/polymer may also comprise one or more salt forming moieties. Preferred salt forming moieties are ammonium and carboxylate. Suitable salts also include any pharmaceutically acceptable acid-addition salts for PEG-oligomers/polymers having a basic amino group and pharmaceutically acceptable salts derived from pharmaceutically acceptable bases for PEG-oligomers/polymers having, e.g., a free carboxy group. Pharmaceutically acceptable salts of the acid may be prepared by treating the free acid with an appropriate base. Pharmaceutically

acceptable base salts include, for example, alkali metal salts such as sodium or potassium, alkaline earth metal salts such as sodium or potassium, alkaline earth metal salts such as calcium or magnesium, and ammonium or alkyl ammonium salts.

4.2 Methods for Producing the Paclitaxel-PEG Conjugates

Paclitaxel is commercially available and can be isolated by methods known in the art from the bark of *Taxus brevifolia*. Paclitaxel can also be isolated from the leaves (or needles) of various *Taxus* species in yields comparable to the yield from *Taxus brevifolia* bark. U.S. Patent 5,019,504 describes tissue-culture methods for producing paclitaxel. It is also known that paclitaxel is produced by the fungus *Taxomyces andreanae*.

Additionally, paclitaxel can be prepared by known synthetic methods, for example, as reported by Holton et al., *J. Am. Chem. Soc.* 116:1597-1598 (1994); Holton et al., *J. Am. Chem. Soc.* 116: 1599-1600 (1994); and Nicolaou et al., *Nature* 367:630-634 (1994).

In the ensuing examples, the n, p, m, R, and R^1 and R^2 symbols are as described above in general Formulae 1-11.

4.2.1 Formula 1

The polymers of Formula 1 are commercially available and/or are readily synthesized by one of skill in the art without undue experimentation.

4.2.2 Formula 2

In the synthesis of the oligomers of Formula 2:

$$—\overset{\overset{\displaystyle O}{\|}}{C}—(CH_2)_n—\overset{\overset{\displaystyle R}{|}}{N}—CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 2)}$$

wherein n is from 1 to 7, m is from 2 to 25, and R is a lower alkyl, it is desirable to start with an ester of a fatty acid having a terminal carbon which bears a primary amino moiety. Such compounds are commercially available. The amino ester in an inert solvent is treated with a solution of monomethoxy polyethylene glycol of appropriate molecular weight bearing an aldehyde terminal carbon, followed by the addition of a solution of sodium borohydride. The product is purified after solvent extraction by column chromatography.

$$\mathrm{CH_3CH_2O_2C(CH_2)_nNH_2 + O{=}CHCH_2(OC_2H_4)_mOCH_3}$$

$$\Big\downarrow \begin{array}{l}\text{1. THF}\\ \text{2. NaBH}_4\end{array}$$

$$\mathrm{CH_3CH_2O_2C(CH_2)_nNHCH_2CH_2(OC_2H_4)_mOCH_3}$$

where n and m are as previously defined.

Sometimes it is desirable to alkylate the secondary amine moiety to form a desired oligomer bearing a tertiary amine. A solution of the oligomer in an inert solvent is treated with one equivalent of alkyl halide. The product is purified after solvent extraction by column chromatography.

$$\mathrm{CH_3CH_2O_2C(CH_2)_nNHCH_2CH_2(OC_2H_4)_mOCH_3}$$

$$\Big\downarrow \text{RBr}$$

$$\mathrm{CH_3CH_2O_2C(CH_2)_nN(R)CH_2CH_2(OC_2H_4)_mOCH_3}$$

The ester is converted to an acid by treating it in an inert solvent with a dilute solution of sodium hydroxide at room temperature. The free acid is purified after solvent extraction by column chromatography. The acid is coupled to the drug after in situ activation.

$$CH_3CH_2O_2C(CH_2)_nN(R)CH_2CH_2(OC_2H_4)_mOCH_3$$

$$\Big\downarrow \text{NaOH}$$

$$HOC(O)(CH_2)_nN(R)CH_2CH_2(OC_2H_4)_mOCH_3$$

$$\Big\downarrow \begin{array}{l}\text{1. Drug-OH}\\ \text{2. dicyclohexylcarbonolamide (DCCE) and}\\ \quad\text{4-dimethylaminopyridine (DMAP)}\end{array}$$

$$Drug{-}OC(O)(CH_2)_nN(R)CH_2CH_2(OC_2H_4)_mOCH_3$$

The drug in these examples can be, for example, paclitaxel or docetaxel.

It is sometimes desirable to synthesize the drug-oligomer by starting with the therapeutic compound derivatized as an ester of fatty acid having a terminal carbon which bears a halide and an appropriate monomethoxy-polyethylene glycol with a terminal carbon bearing a primary amino moiety. The polyethylene glycol reagent is dissolved in an inert solvent at room temperature. An equivalent amount of the drug-halide is dissolved in an inert solvent and added slowly to the solution of polyethylene glycol. The product is purified after solvent extraction using column chromatography.

$$D{-}O_2C(CH_2)_nCH_2Br + NH_2CH_2CH_2(OC_2H_4)_mOCH_3$$

$$\Big\downarrow \text{THF}$$

$$D{-}O_2C(CH_2)_nCH_2NHCH_2CH_2(OC_2H_4)_mOCH_3$$

The ester is hydrolyzed with a dilute solution of sodium hydroxide as in the previous procedure and coupled to the drug (e.g., paclitaxel or docetaxel) after *in situ* activation as in the previous example.

4.2.3 **Formula 3**

In the synthesis of the oligomer of Formula 3:

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2)_p-\overset{R}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 3)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, and R is a lower alkyl, it is desirable to start with a half-ester of a dicarboxylic acid of an aliphatic compound and an amino-containing polyethylene. In the synthesis of the amino-containing polyethylene, an appropriate molecular weight monomethyl polyethylene glycol having an aldehyde moiety at the terminal end is treated in an inert solvent with an aliphatic compound bearing amino moieties at the two terminal carbons. One amino moiety is protected with tert-butoxycarbonyl while the free amine reacts with the aldehyde moiety. The product is purified after solvent extraction column chromatography. The product is deprotected by treating in an inert solvent with trifluoroacetic acid, neutralizing the acid and purifying after solvent extraction using column chromatography.

$$\mathbf{(CH_3)_3C{-}OC(O)NH(CH_2)_pNH_2 + O{=}CHCH_2(OC_2H_4)_mOCH_3}$$

$$\downarrow$$

$$\mathbf{(CH_3)_3C{-}OC(O)NH(CH_2)_pN{=}CHCH_2(OC_2H_4)_mOCH_3}$$

$$\downarrow \textbf{TFA}$$

$$\mathbf{NH_2(CH_2)_pN{=}CHCH_2(OC_2H_4)_mOCH_3}$$

The half ester in an inert solvent is treated with a solution of the amino-derivatized polyethylene glycol at room temperature after an *in situ* activation of the acid. The product is purified by column chromatography after solvent extraction. The imino moiety is reduced by treating with a solution of sodium borohydride and purified as in the previous procedure.

It is sometimes desirable to alkylate the secondary amine. To achieve this end, the oligomer is dissolved in an inert solvent and treated with a solution of an alkyl halide in an inert solvent.

The ester is hydrolyzed, activated *in situ*, and coupled to the therapeutic compound (e.g., paclitaxel or docetaxel).

$$NH_2(CH_2)_pN{=}CHCH_2(OC_2H_4)_mOCH_3 + CH_3CH_2O_2C(CH_2)_nC(O)OH$$

$$\Big\downarrow \text{DCC/DMAP}$$

$$CH_3CH_2O_2C(CH_2)_nC(O)NH(CH_2)_pN{=}CHCH_2(OC_2H_4)_mOCH_3$$

$$\Big\downarrow \text{NaBH}_4\text{/R Br}$$

$$CH_3CH_2O_2C(CH_2)_nC(O)NH(CH_2)_pNRCHCH_2(OC_2H_4)_mOCH_3$$

$$\Big\downarrow \text{NaOH}$$

$$HOC(CH_2)_nC(O)NH(CH_2)_pNRCHCH_2(OC_2H_4)_mOCH_3$$

$$\Big\downarrow \text{Drug-OH/DCC/DMAP}$$

$$DOC(CH_2)_nC(O)NH(CH_2)_pNRCHCH_2(OC_2H_4)_mOCH_3$$

where D indicates the drug component of the drug-amphiphile conjugate. The amphiphilic drug conjugate is converted to a salt form to improve aqueous solubility as necessary using a pharmaceutically acceptable acid.

4.2.4 Formula 4

The procedure for the synthesis of the oligomer of Formula 4:

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-CH_2CH_2(OC_2H_4)_r-\overset{R}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 4)}$$

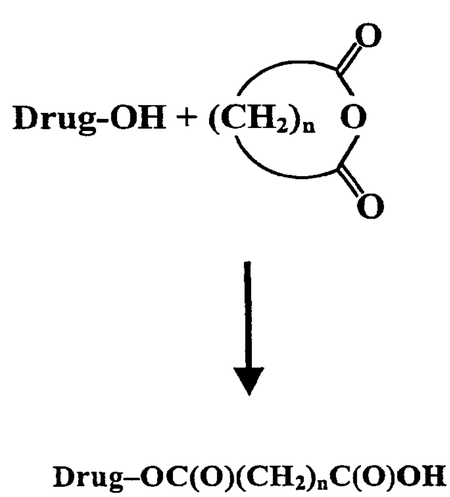
wherein n is from 1 to 6, m and r are each independently from 2 to 25, and R is a lower alkyl, is the same as for the oligomer of Formula 3 with the exception that the aliphatic diamino moieties are replaced with polyethylene glycol diamine.

4.2.5 Formula 5

In the synthesis of a prodrug comprising the oligomer of Formula 5:

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2)_p-\overset{R}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mNH_2 \qquad \text{(Formula 5)}$$

wherein n is from 1 to 6, p is from 2 to 8 and m is from 2 to 25 and R is a lower alkyl, the drug bearing a hydroxyl moiety is treated in an inert solvent with an aliphatic acid anhydride to form a half ester. The half-ester is dissolved in an inert solvent, activated and treated with one equivalent of a polyethylene glycol of appropriate molecular weight, in which the terminal hydroxyl moieties are replaced with amino moieties.



$$\downarrow$$

1. 1,1'-carbonyldiimidizole (CDI)
2. $NH_2(CH_2)_pNRCH_2CH_2(OC_2H_4)_mNHC(O)OC(CH_3)_3$
3. TFA/Basic Column

$$\textbf{Drug–}OC(O)(CH_2)_nC(O)NH_2CH_2CH_2(OC_2H_4)_mNH_2$$

where all substituent groups (e.g., n, m and p) are as previously defined.

4.2.6 Formula 6

The oligomer of Formula 6:

$$-\overset{\displaystyle O}{\overset{\|}{C}}-(CH_2)_n-\overset{\displaystyle O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2)_p-\overset{\displaystyle R}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mNH_3^+X^- \qquad \text{(Formula 6)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, X^- is a negative ion, is prepared by treating the compound represented by Formula 5 with a pharmaceutically acceptable acid to obtain the appropriate salt. The salt increases the water-solubility of the amphiphilic drug conjugate.

4.2.7 Formula 7

The synthesis of the oligomer of Formula 7:

$$-\overset{\displaystyle O}{\overset{\|}{C}}-(CH_2)_n-\overset{\displaystyle O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2)_p-\overset{\displaystyle R^1}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mNHR^2 \qquad \text{(Formula 7)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, and R^1 and R^2 are each independently a lower alkyl, is analogous to the synthesis of the oligomer of Formula 5, with the exception that the end-terminal amino moiety is alkylated with the halide of a short chain alkyl group such as methyl, ethyl, propyl, isopropyl or *t*-butyl before reacting to the half-ester of the drug.

$$(CH_3)_3COC(O)NH_2(CH_2)_pBr + NH_2CH_2CH_2(OC_2H_4)_mNH_2$$

$$\downarrow$$

$$(CH_3)_3COC(O)NH_2(CH_2)_pNHCH_2CH_2(OC_2H_4)_mNH_2$$

$$\Bigg\downarrow \quad \begin{array}{l} 1.\ \text{RBr} \\ 2.\ \text{TFA} \\ 3.\ \text{Basic Column} \\ 4.\ \text{D–}O_2C(CH_2)_nCO_2H/\text{DCC} \end{array}$$

$$\text{D–}OC(O)(CH_2)_nC(O)NH(CH_2)_pNRCH_2CH_2(OC_2H_4)_mNHR$$

where n, m and R are as previously defined.

4.2.8 Formula 8

In the synthesis of the oligomer of Formula 8:

$$-\overset{\overset{\large O}{\|}}{C}-(CH_2)_n-\overset{\overset{\large O}{\|}}{C}-\overset{H}{N}-CH_2CH_2(OC_2H_4)_mOCH_2-\overset{\overset{\large O}{\|}}{C}-NH(CH_2)_pN(CH_3)_2 \quad \text{(Formula 8)}$$

wherein n is from 1 to 6, p is from 2 to 8 and m is from 2 to 25, the half-ester of the aliphatic dicarboxylic acid is treated in an inert solvent with polyethylene glycol that has already been derivatized with amino moieties, after *in situ* activation.

$$CH_3CH_2OC(O)(CH_2)_nC(O)OH$$

$$+$$

$$NH_2CH_2CH_2(OCH_2CH_2)_mOCH_2C(O)NH(CH_2)_pN(CH_3)_2$$

$$\Bigg\downarrow \ 1.\ \text{DCC; } 2.\ \text{NaOH}$$

$$HOC(O)(CH_2)_nC(O)NHCH_2CH_2(OCH_2CH_2)_mOCH_2C(O)NH(CH_2)_pN(CH_3)_2$$

The amino-derivatized polyethylene glycol is prepared from an N-protected polyethylene glycol amino acid.

$$\text{tert-BOC}NHCH_2CH_2(OCH_2CH_2)_mOCH_2C(O)\text{–}OH + NH_2(CH_2)_pN(CH_3)_2$$

$$\Big\downarrow \text{DCC/DMAP}$$

$$\text{tert-BOCNHCH}_2\text{CH}_2(\text{OCH}_2\text{CH}_2)_m\text{OCH}_2\text{C(O)–NH(CH}_2)_p\text{N(CH}_3)_2$$

$$\Big\downarrow \text{TFA/Basic Column}$$

$$\text{NH}_2\text{CH}_2\text{CH}_2(\text{OCH}_2\text{CH}_2)_m\text{OCH}_2\text{C(O)–NH(CH}_2)_p\text{N(CH}_3)_2$$

The primary amino moiety is deprotected with trifluoroacetic acid and basified before treating with the half-ester.

4.2.9 Formula 9

In the synthesis of the oligomer of Formula 9:

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n(OC_2H_4)_mO(CH_2)_p-\overset{\overset{\displaystyle O}{\|}}{C}-O^-X^+ \quad \text{(Formula 9)}$$

wherein n and p are each independently from 1 to 6, m is from 2 to 25 and X^+ is a positive ion, the starting acid is commercially available. It is sometimes desirable to prepare the diacid. To achieve this end, the appropriate modified polyethylene glycol oligomer is treated in an inert solvent with sodium hydride and an ester of a fatty acid bearing a halide moiety at the terminal carbon. The carboxylic acid diester is hydrolyzed in a dilute solution of sodium hydroxide and coupled to the drug moiety after *in situ* activation. The desired product is separated and purified by column chromatography.

$$\text{CH}_3\text{CH}_2\text{O}_2\text{C(CH}_2)_n\text{Br}$$

$$+$$

$$\text{HOCH}_2\text{CH}_2(\text{OC}_2\text{H}_4)_m\text{O(CH}_2)_p\text{CO}_2\text{CH}_2\text{CH}_3$$

$$\big\downarrow \text{2NaH/THF}$$

$$\mathbf{CH_3CH_2O_2C(CH_2)_n(OCH_2CH_2)_mO(CH_2)_pCO_2CH_2CH_3}$$

$$\big\downarrow \text{NaOH}$$

$$\mathbf{HOC(O)(CH_2)_n(OCH_2CH_2)_mO(CH_2)_pC(O)OH}$$

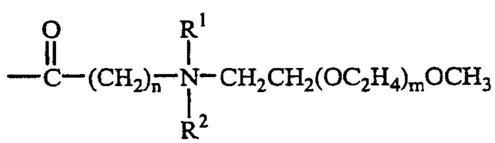
$$\big\downarrow \begin{array}{l}\text{Drug-OH/CH}_2\text{Cl}_2\\ \text{DCC/DMAP}\end{array}$$

$$\mathbf{Drug\text{–}OC(O)(CH_2)_n(OCH_2CH_2)_mO(CH_2)_pC(O)OH}$$

where n, m and p are as previously defined.

4.2.10 Formula 10

The synthesis of the oligomer of Formula 10:

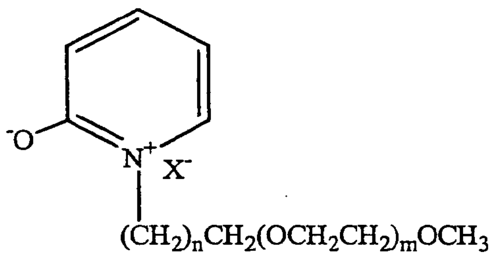


(Formula 10)

wherein n is from 1 to 5, m is from 2 to 25, and wherein R^1 and R^2 are each independently lower alkyl, is analogous to the synthesis of the oligomer of Formula 2, with the exception that the amino moiety is quaternized with short-chain aliphatic moieties. It is noted that the methoxy moiety can include other short chain (1 to 6 carbons) aliphatic moieties.

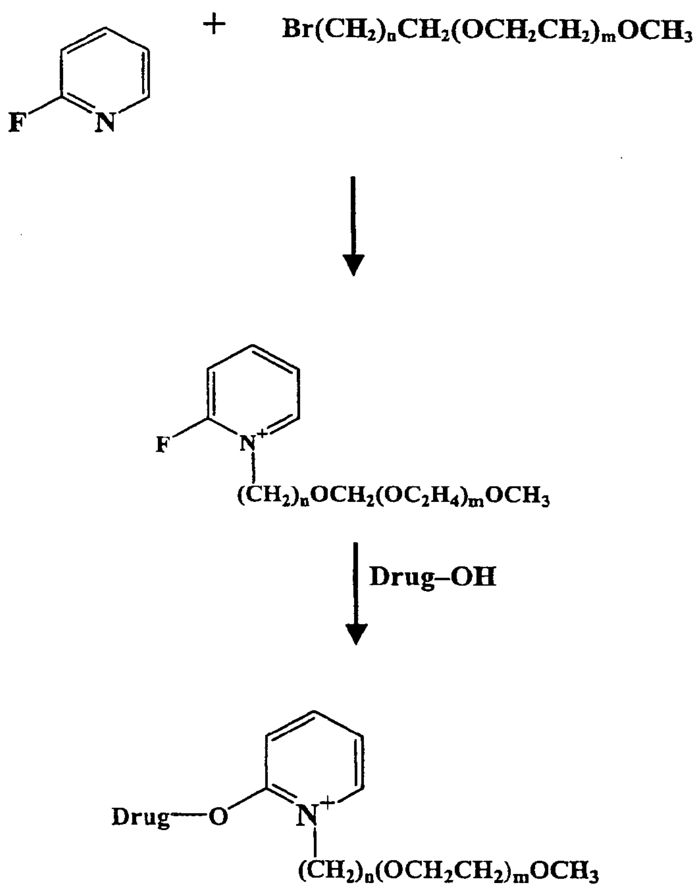
4.2.11 Formula 11

In the synthesis of the oligomers of Formula 11:



(Formula 11)

wherein n is from 1 to 6, m is from 2 to 25 and X^- is a negative ion, a 2-fluoro- or 4-fluoro-pyridine is treated in an inert solvent with a monomethoxypolyethylene glycol having a terminal carbon bearing a halide, tosylate or mesylate ion. This pyridinium derivative is precipitated and triturated with an appropriate solvent and dried. The salt in an inert solvent is treated with drug, such as paclitaxel or docetaxel, in the presence of a quaternary-salt compound forming base, to yield a polyethylene glycol pyridinium derivative.



4.2.12 Attachment of PEG Polymers/Oligomers to Taxane Parent

The oligomers are suitably attached to the taxane parent at any of the hydroxyl substituents of the taxane parent. Where the taxane parent is paclitaxel, docetaxel, or an analog thereof, the oligomers are preferably attached at one or more of the following positions: the C-2' hydroxyl group; the C-7 hydroxyl group; and the C-1 hydroxyl group. In a preferred mode, only one oligomer is present, and the oligomer is attached at the C-2' hydroxyl group. It will be appreciated by those of skill in the art that a solution of taxane prodrugs according to the present invention where the taxane is paclitaxel, docetaxel or the like may comprise a mixture of mono-, di-, and/or tri-substituted taxane prodrugs.

The PEG-oligomers/polymers of the present invention can be attached to the taxane compound to provide the taxane prodrugs of the invention according to the following general synthetic procedure. The taxane compound is dissolved in a substantially dry organic solvent, e.g., chloroform. Pyridine or another quaternary-compound forming agent is added to the foregoing mixture. Activated PEG-oligomer/polymer is added dropwise and the mixture is stirred for 3-5 hours. Then reaction mixture is washed with 1% H_2SO_4 and deionized water, dried over $MgSO_4$ and concentrated. The residue is chromatographed on silica gel column, using for example, chloroform-methanol (90%-10%) as developing agent. The fractions containing the desired prodrugs are collected, concentrated, and dried. Product is characterized by TLC, HPLC, NMR, and/or MS.

4.3 Pharmaceutical Compositions and Methods of Use

The pharmaceutical compositions containing the novel prodrugs as active ingredients may be any pharmaceutically acceptable dosage forms known in the art which do not completely diminish the activity of the taxane prodrugs. Examples include oral, injectable or intravenous dosage forms. Each dosage form comprises an effective amount of a prodrug of the invention and pharmaceutically inert ingredients, e.g., conventional excipients, vehicles, fillers, binders, disintegrants, solvents, solubilizing agents, sweeteners, coloring agents and any other active or inactive ingredients which are regularly included in pharmaceutical dosage forms. Suitable oral dosage forms include tablets, capsules, caplets, gelcaps, pills, liquid solutions, suspensions or elixirs, powders, lozenges, micronized particles and osmotic delivery systems. Suitable injectable and IV dosage forms include isotonic saline solutions or dextrose solutions containing suitable buffers and preservatives. Many such dosage forms and vehicles, and listings of inactive

ingredients are well known in the art and are set forth in standard texts such as *The Pharmaceutical Codex: Principles and Practice of Pharmaceutics*, 12th edition (1994).

The taxane prodrugs of the present invention can be administered in such oral (including buccal and sublingual) dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in nasal, ophthalmic, otic, rectal, topical, intravenous (both bolus and infusion), intraperitoneal, intraarticular, subcutaneous or intramuscular inhalation or insufflation form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

The dosage regimen utilizing the taxane prodrugs of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral administration is generally preferred for administration to a human. In some cases, a relatively lower dose is sufficient and, in some cases, a relatively higher dose or increased number of doses may be necessary. Topical application similarly may be once or more than once per day depending upon the usual medical considerations. Advantageously, taxane prodrugs of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily.

In the methods of the present invention, the taxane prodrugs can form the active ingredient and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible

carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture as described above and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the taxane prodrug, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The taxane prodrugs of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving

the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or saccharin, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The taxane prodrugs of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Taxane prodrugs of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The taxane prodrugs of the present invention may also be coupled with soluble polymers, such as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepoly-lysine substituted with palmitoyl residues. Furthermore, the taxane prodrugs of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, cross-linked or amphipathic block copolymers of hydrogels, polyaspartic acid or polyglutamic acid.

The present invention includes pharmaceutical compositions containing about 0.01 to about 99.5%, more particularly, about 0.5 to about 90% of a taxane prodrug in combination with a pharmaceutically acceptable carrier.

Parenteral administration can be effected by utilizing liquid dosage unit forms such as sterile solutions and suspensions intended for subcutaneous, intramuscular or intravenous injection. These are prepared by suspending or dissolving a measured amount of the taxane prodrug in a non-toxic liquid vehicle suitable for injection such as aqueous oleaginous medium and sterilizing the suspension or solution.

Alternatively, a measured amount of the taxane prodrug is placed in a vial and the vial and its contents are sterilized and sealed. An accompanying vial or vehicle can be provided for mixing prior to administration. Non-toxic salts and salt solutions can be added to render the injection isotonic. Stabilizers, preservations and emulsifiers can also be added.

Rectal administration can be effected utilizing suppositories in which the taxane prodrug is admixed with low-melting water-soluble or insoluble solids such as polyethylene glycol, cocoa butter, higher ester as for example flavored aqueous solution, while elixirs are prepared through myristyl palmitate or mixtures thereof.

Topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

For administration by inhalation the taxane prodrugs according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The preferred pharmaceutical compositions are those in a form suitable for oral administration, such as tablets and liquids and the like and topical formulations.

The present invention also provides a method of treating a mammalian subject having a tumor, cancer, or other disease condition responsive to a taxane (e.g., paclitaxel or docetaxel). This treatment method comprises administering to said subject a pharmaceutical composition containing a pharmaceutically effective amount of a taxane-oligomer prodrug according to the present invention. Taxane-responsive diseases which may be treated by the invention include cancers, tumors, malignancies, uncontrolled tissue or cellular proliferation secondary to tissue injury,

polycystic kidney disease and malaria. Among the cancers which may be treated are hepatocellular carcinoma, liver metastases, gastrointestinal cancers, lymphoma, leukemia, melanoma, Kaposi's sarcoma, and cancers of the pancreas, kidney, cervix, breast, ovary, brain, prostate, and urogenital carcinoma.

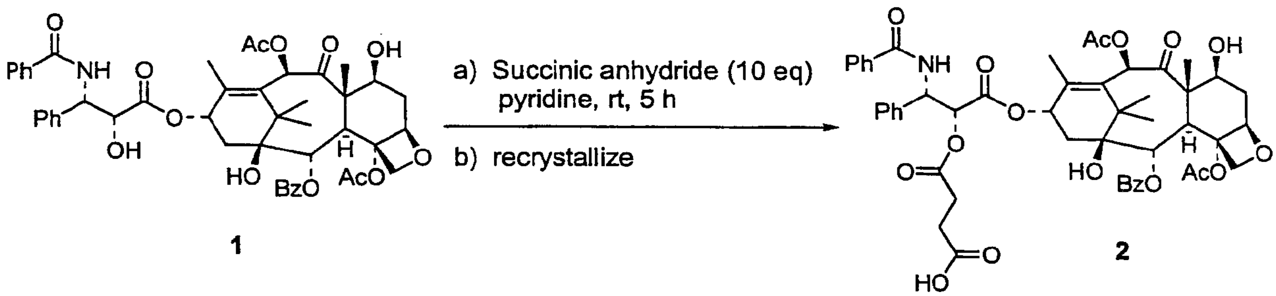
The taxane prodrugs of the invention may be administered by intravenous administration, infusion, non-intravenous injection, intraperitoneally and by injection of a bolus. The taxane prodrugs may also be administered orally to the patient in a suitable dosage form alone or together with an oral bioavailability-enhancing agent. Such bioavailability-enhancing agent may be selected from the group consisting of cyclosporins A through Z, (Me-lle-4)-cyclosporin, dihydro cyclosporin A, dihydro cyclosporin C, acetyl cyclosporin A, genistein and related isoflavonoids, quercetin, calphostin, ceramides, morphine and morphine congeners. Preferred enhancing agents are cyclosporin A, cyclosporin C, cyclosporin D, cyclosporin F, dihydro cyclosporin A, dihydro cyclosporin C, acetyl cyclosporin A, and B cyclodextrin.

Further, the taxane prodrugs of the present invention may be administered alone or with other chemotherapeutic agents (e.g., anti-cancer agents). Where the paclitaxel-PEG prodrugs of the present invention are administered with other chemotherapeutic agents, the paclitaxel-PEG prodrugs and other chemotherapeutic agents may be administered simultaneously or sequentially. Additionally, the paclitaxel-PEG prodrugs of the present invention may be administered before, after or simultaneously with radiation therapy.

In one aspect, the present invention provides a treatment for cancer comprising administering to a subject a combination of the taxane prodrugs of the present invention and cisplatin. Preferably the cancer is ovarian cancer, and preferably the taxane prodrug comprises paclitaxes and is administered before cisplatin. Paclitaxel has been shown to be effectively administered with cisplatin. Neutropenia has been shown to be a dose limiting effect of coadministration of paclitaxel and cisplatin. Clinical trials have demonstrated that less neutropenia occurs when paclitaxel is administered before cisplatin. For example, while preferred doses of paclitaxel-PEG prodrug are up to 350 mg/m^2 followed by cisplatin ($75mg/m^2$), more preferred doses are paclitaxel-PEG prodrug (25mg/ml), followed by cisplatin (75mg/ml) and G-CSF at standard doses (5μg/kg/d subcutaneously).

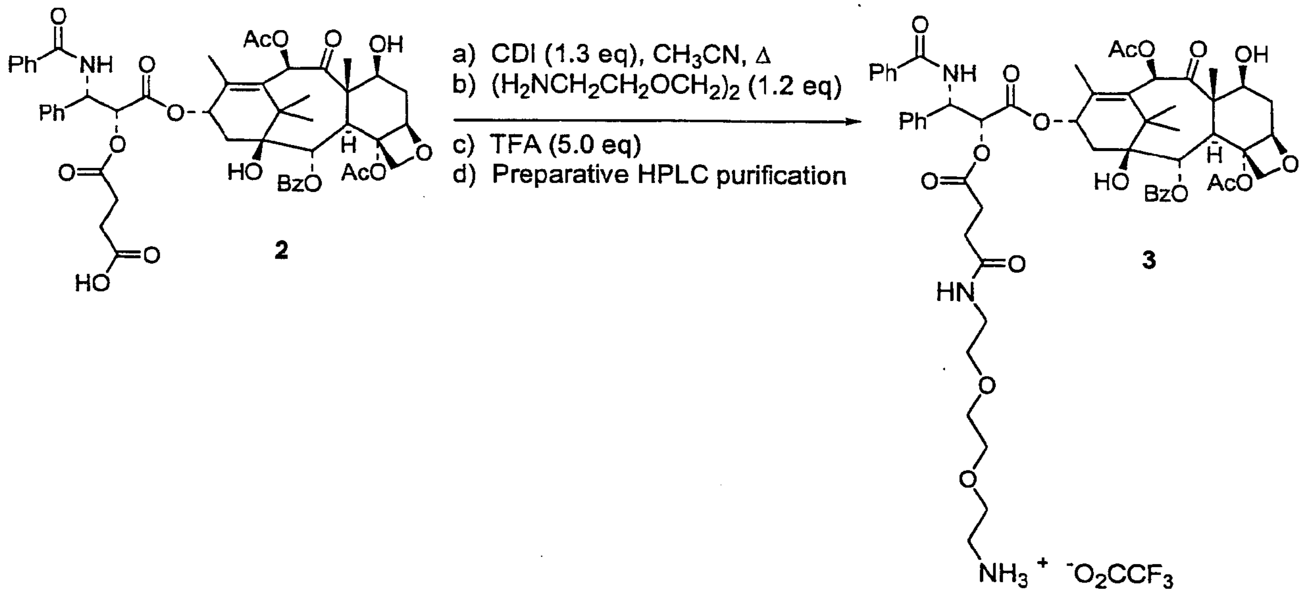
5. Examples

5.1 2'-Succinylpaclitaxel



The following protocol is an improved version of the procedure of Deutsch, *et. al.* To a mixture of 5.00 g (5.86 mmol) of paclitaxel and 5.86 g (58.6 mmol) of succinic anhydride was added 110 mL of anhydrous pyridine. After stirring the resulting solution at room temperature for 5 h, thin layer chromatography (TLC) analysis indicated complete consumption of the paclitaxel. The solvent was removed under reduced pressure by means of rotary evaporation and the residue was dried *in vacuo* for 2 h. The resulting waxy semisolid was stirred efficiently with 200 mL of water, affording a flocculent white solid, which was collected by suction filtration on a Buchner funnel. The solid was washed with water then allowed to suck dry for 30 min., then dried at room temperature *in vacuo* in a dessicator over P_2O_5 for 15 h. The white solid was taken up in 30 mL of acetone, then with efficient stirring, 30 mL of water was slowly added. The resulting thick white paste was well-blended for 15 min, suction filtered through a Buchner funnel rinsing with excess water, and allowed to suck dry for 1 h. The resulting moist white solid was carefully dried at room temperature *in vacuo* in a dessicator over P_2O_5 for 18 h. As the solid became more dry and less coagulated during this drying period, the P_2O_5 was replenished and the solid was periodically broken into smaller pieces until a moderately fine powder was obtained (5.29 g, 95% yield). Analytical HPLC analysis indicated this material to be of 97% purity. MS (FAB+) *m/z* (rel. inten.) 954 (M^+, 100), 570 (15), 509 (64).

5.2 2'-Succinamidyl-PEG2-amine-paclitaxel trifluoroacetate



A mixture of 200 mg (0.210 mmol) of 2'-succinylpaclitaxel (Compound 2) and 47 mg (0.273 mmol, 95% purity) of 1,1'-carbonyldiimidazole under nitrogen was dissolved in 2.9 mL of anhydrous acetonitrile. A gas outlet needle was inserted through the reaction flask septum such that a moderate flow of nitrogen was maintained to flush out carbon dioxide gas. The reaction vessel was lowered into an oil bath preheated to 48°C, causing gas evolution. After stirring efficiently for 15 min, the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The amount of acetonitrile lost to evaporation was replenished. The nitrogen outlet needle was removed such that a static atmosphere of nitrogen was maintained. A solution of 37 μL (0.252 mmol) of 2,2'-(ethylenedioxy)bis(ethylamine) in 1.4 mL of acetonitrile was added dropwise. After 45 min., a solution of 81 μL (1.05 mmol) of trifluoroacetic acid in 0.7 mL of acetonitrile was added dropwise. The resulting crude reaction solution typically contains a 70-74% yield of the desired trifluoroacetate product (Compound 3), as determined by analytical HPLC analysis.

5.3 Preparative HPLC Purification of Trifluoroacetate (Compound 3)

The product was generally purified by prep HPLC by combining the product-containing fractions.

5.3.1 Improving HPLC Resolution

Medium Scale Reaction. To improve HPLC resolution on a medium scale, the crude reaction solution was diluted by adding water without causing precipitation. Thus, to an aliquot of 3.30 mL of the above reaction solution was slowly added 4.03 mL of water with efficient stirring, consequently affording a solution consisting of 55% water. The resulting slightly hazy mixture was filtered through a 0.45 μm Gelman acrodisc 13 syringe filter, then chromatographed on a Waters 600E HPLC system using a reverse phase Vydac column (22 mm x 250 mm, C18, 300Å, 10-15μ). The mobile phase was an acetonitrile-water solution containing 0.1% (v/v) trifluoroacetic acid. Major fractions containing desired product of >97% purity were obtained using a gradient elution, from 40:60 to 45:55, acetonitrile:water with 0.1% (v/v) TFA over 30 minutes at a flow rate of 5 mL/min. Subsequent isocratic elution with 90:10, acetonitrile:water containing 0.1% (v/v) TFA removed unidentified side products in preparation for subsequent chromatographic runs.

For analytical purposes, the purified fractions resulting from the above-described amidation reaction protocol [200 mg (0.210 mmol) scale of 2'-succinylpaclitaxel (2)] were concentrated under reduced pressure by means of rotary evaporation with gradual bath warming to 55°C, then dried *in vacuo* at room temperature to obtain 170 mg (68% yield) of trifluoroacetate (Compound 3) as an amorphous white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (2H, d, J=7.2 Hz), 7.99-7.81 (2H, m), 7.66-7.20 (11H, m), 6.92 (1H, brs), 6.28 (1H, s), 6.07 (1H, t, J=10.0 Hz), 5.86 (1H, dd, J=3.9, 5.0 Hz), 5.65 (1H, d, J=6.9 Hz), 5.42 (1H, d, J=5.4 Hz), 4.94 (1H, d, J=8.2 Hz), 4.36 (1H, m), 4.29 (1H, d, J=8.5 Hz), 4.16 (1H, d, J=8.5 Hz), 3.74 (1H, d, J=6.9 Hz), 3.66-3.04 (16H, m), 2.80-2.60 (2H, m), 2.38 (3H, s), 2.20 (3H, s), 1.84 (3H, s), 1.66 (3H, s), 1.20 (3H, s), 1.13 (3H, s); MS (FAB+) *m/z* 1084 (M^+).

Larger Scale Reaction. A larger scale amidation reaction solution consisting of 1,000 mg (1.05 mmol) of 2'-succinylpaclitaxel (Compound 2), 27 mL total volume was shown to contain 44% of desired trifluoroacetate product (Compound 3) by analytical HPLC analysis. A 10.0 mL aliquot was concentrated under reduced pressure by means of rotary evaporation just to the point of affording a slightly viscous yellow oil. The oil was dissolved by adding 1.0 mL of acetonitrile, filtered through a 0.45 μm Gelman acrodisc 13 syringe filter, then chromatographed on a Waters 600E HPLC system using a reverse phase Vydac column (50 mm x 250 mm, C18, 300Å, 10-15μ). The mobile phase was an acetonitrile-water solution containing 0.1 % (v/v) trifluoroacetic acid. Major fractions containing desired product of >97% purity were obtained using a gradient elution, from 40:60 to 45:55, acetonitrile:water with 0.1% (v/v) TFA over 30 minutes at a flow rate of 26

mL/min. Subsequent isocratic elution with 90:10, acetonitrile:water containing 0.1% (v/v) TFA removed unidentified side products in preparation for subsequent chromatographic runs.

The fractions determined by analytical HPLC analysis to be of high purity were combined with analogous preparative HPLC runs to provide a combined solution of 870 mL total volume containing trifluoroacetate (Compound 3) of >97% purity. The solution was used directly (without concentration) in the ion exchange chromatography step.

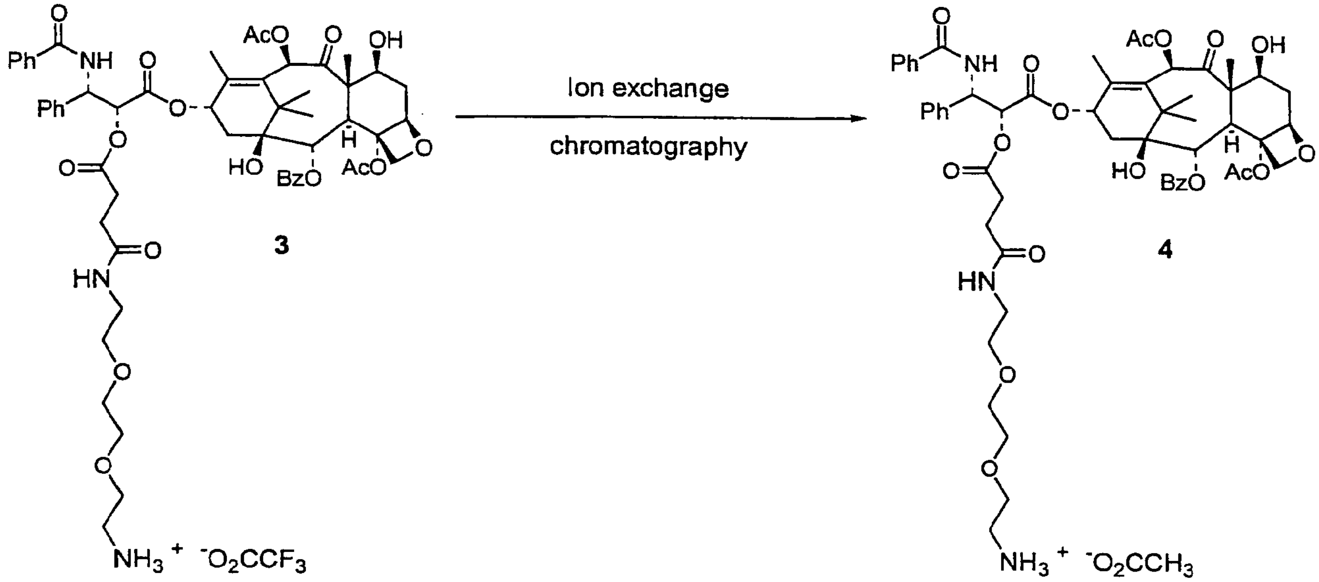
5.4 Stability of Trifluoroacetate (Compound 3)

It was observed that several trifluoroacetate product fraction solutions obtained from a preparative HPLC run initially of an average purity of 98.8% changed to an average of 97.4% purity after storage at 8°C for 16 days, as determined by analytical HPLC analysis.

5.4.1 Determination of Aqueous Solubility of Trifluoroacetate (Compound 3)

To a sample of 2.5 mg of trifluoroacetate (Compound 3) in a small vial was added 200 μL of deionized water. The vial was capped and the resulting mixture was ultrasonicated for 15 minutes. The resulting cloudy mixture was filtered through a 0.45 μ Gelman acrodisc 13 syringe filter. The filtrate was weighed (140 mg) and was lyophilized to provide 1.4 mg of a white fluffy solid. Thus, assuming that the aqueous solution is of density 1.00, the water solubility of trifluoroacetate (Compound 3) is 7.4 mg/mL (i.e. 1.4 mg/0.190 mL).

5.5 Ion Exchange Chromatography of Trifluoroacetate Anion for Acetate Anion: Acetate Prodrug (Compound 4)



For preparative purposes, fraction solutions of trifluoroacetate (Compound 3) of >97% purity obtained from a preparative HPLC purification protocol described above were combined and taken on directly to ion chromatography without concentration. For example, combined preparative HPLC fractions of 870 mL total volume theoretically containing 0.462 mmol of substrate and containing 11.3 mmol of TFA (0.1 % (v/v)) was used for the following ion exchange protocol:

A 92 g portion of DOWEX® 1 x 8-400 (strongly basic, chloride form) ion exchange resin was washed three times with 270 mL each of deionized water, each time decanting away the yellow suspended matter and the bulk of the rinse water. To obtain the resin in its acetate form, the resulting slurry was stirred with a solution of 1,882 g of $NaOAc{\cdot}3H_2O$ in 4.00 L of deionized water for 1.0 h. The resin was collected by suction filtration on a Buchner funnel and washed several times with a total of 1.84 L of deionized water. The resin was washed two times with 750 mL each of 0.013 M HOAc (aq) [i.e. 0.1% (v/v) HOAc, by analogy to 0.1% (v/v) TFA used in the preparative HPLC protocols], suction filtered on a Buchner funnel, then allowed to suck dry for 10 min. The resin was suspended in 0.013 M HOAc (aq), poured into a glass flash chromatography column, then eluted using gentle air pressure with 200 mL of 0.013 M HOAc (aq), thus giving a 10 cm high x 3.8 cm diameter resin column, which was then topped off with *ca.* 4 cm of sand. The column was then eluted with 250 mL of acetonitrile, then with 250 mL of 0.013 M HOAc (aq). The 870 mL volume of the trifluoroacetate (3) solution was made to be 0.013 M in HOAc by the

addition of a solution of 0.63 mL of glacial acetic acid in 10 mL of acetonitrile with efficient stirring. The solution was applied to and eluted through the column using gentle air pressure. Fraction collection was commenced immediately using 50 mL test tubes. Once the entire 870 mL of solution had completely passed into/through the resin, the column was further eluted with 0.013 M HOAc (aq). The fractions containing product of >97% purity (as determined by analytical HPLC analysis at 210 nm) were combined and concentrated under reduced pressure by means of rotary evaporation with gradual bath warming to 55°C and dried *in vacuo* at room temperature for 16 h to provide an off-white amorphous residue. The residue was scraped with a spatula from the flask into a fine amorphous powder. The remnants not scraped out of the flask could be further procured without alteration of product purity by transferring to a smaller flask with the aid of a minimal amount of 0.013 M HOAc (aq) as solvent, concentrating as described above, then scraping with a spatula to provide additional product, which was combined and dried at room temperature *in vacuo* in a dessicator over P_2O_5 for 24 h to provide acetate prodrug (Compound 4) (293 mg, 24% unoptimized yield overall of material of >97% purity) as a yellow powder. Combination of the fractions of <97% purity in a manner similar to the method described above afforded 146 mg (12% unoptimized yield) of additional acetate (Compound 4). Analyses of the products by analytical ion chromatography [Quantitative Technologies, Inc., (QTI)] did not show the presence of any trifluoroacetic acid (TFA analysis: below detection limit of 100 ppm). mp 114-117°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (2H, d, J=7.2 Hz), 7.85 (2H, d, J=7.7 Hz), 7.62-7.36 (11H, m), 6.29 (1H, s), 6.11 (1H, t, J=10.0 Hz), 5.87 (1H, dd, J=3.9, 4.4 Hz), 5.65 (1H, d, J=6.9 Hz), 5.44 (1H, d, J=4.9 Hz), 4.95 (1H, d, J=9.5 Hz), 4.38 (1H, m), 4.28 (1H, d, J=8.5 Hz), 4.18 (1H, d, J=8.2 Hz), 3.76 (1H, d, J=6.4 Hz), 3.63-3.34 (16H, m), 3.04 (2H, brs), 2.75 (2H, m), 2.53 (2H, m), 2.40 (3H, s), 2.20 (3H, s), 2.01 (3H, s), 1.87 (3H, s), 1.67 (3H, s), 1.20 (3H, s), 1.13 (3H, s); MS (FAB+) *m/z* (rel. inten.) 1084 (M^+).

5.6 General Solubility of Acetate (Compound 4)

Acetate (Compound 4) is highly soluble in $CDCl_3$ and sparingly soluble in diethyl ether and in hexanes. Three separate samples of 3.0 mg each of acetate (Compound 4) afforded a homogeneous solution in 81 μL of 100% anhydrous ethanol, in 81 μL of acetone, and in 81 μL of 0.5 M aqueous acetic acid. Thus, the solubility in each of these three solvents must be some value equal to or greater than 37 mg/mL (i.e. 3.0 mg/ 0.081 mL).

5.7 Determination of Aqueous Solubility of Acetate (Compound 4) by Mass

To a sample of 10.0 mg of acetate (Compound 4) in a small vial was added 176 μL of deionized water. The vial was capped and the resulting mixture was ultrasonicated for 15 minutes. The resulting liquid was shown to contain acetate (Compound 4) in 98.7% purity by analytical HPLC analysis at 210 nm. The liquid was filtered through a 0.45 μ cellulose acetate syringe filter. The mass (76mg) of a known volume (75 μL) of the filtrate was measured to determine that the density of the solution was 1.01 g/mL. The filtrate was shown to contain acetate (Compound 4) in 98.8% purity by analytical HPLC analysis at 210 nm. A 118 mg quantity of the filtrate was lyophilized to provide 6.4 mg of an off-white fluffy solid. Thus, by this method the water solubility of acetate (Compound 4) was determined to be 55 mg/mL (i.e. 6.4 mg/0.117 mL).

5.8 Determination of Aqueous Solubility of Acetate (Compound 4) by Analytical HPLC

To a sample of 10.0 mg of acetate (Compound 4) in a small vial was added 150 μL of deionized water. The vial was capped, vortexed for 3 min., and ultrasonicated for 15 minutes. The resulting viscous pale yellow/orange mixture was slowly and carefully taken up into a 1 mL syringe and then firmly filtered through a 0.45 μ cellulose acetate syringe filter, thus affording a viscous homogeneous yellow/orange solution. A 75 μL portion of the filtrate was diluted 88-fold with acetonitrile and then analyzed by analytical HPLC at 229 nm and 270 nm. The area under the curve observed at 229 nm and 270 nm was respectively compared to both a 3-point calibration curve obtained at 229 nm (r^2 = 0.99999) and a 5-point curve obtained at 270 nm (r^2 = 0.99996). Thus, by this method, the water solubility of acetate (Compound 4) was determined to be 40.1 mg/mL (at 229 nm) and 39.7 mg/mL (at 270 nm).

5.9 Chemical Hydrolysis Behavior of Acetate (Compound 4)

A sample of solid acetate (Compound 4) was dissolved (*ca.* 1 mg/mL) in wet acetonitrile (nonanhydrous due to exposure to humid air). Over the course of 26 days at room temperature, acetate (Compound 4) smoothly converted quantitatively into paclitaxel (1) with no significant side product formation, as observed by analytical HPLC analysis (see Figure 1).

5.9.1 Chemical Hydrolysis Behavior of Acetate (Compound 4) at Various pH

To many 13 mm x 100 mm glass test tubes was added 5.15 μL each of an 8.741×10^{-4} M aqueous solution of acetate prodrug (Compound 4). To each tube was then added 295 μL of aqueous

solutions of phosphate buffered saline (PBS) of pH 8.00, 7.40, 7.00 and 5.80 and an acetic acid/formic acid buffered solution of pH 2.00. The tubes were capped and incubated at 37°C in a reciprocal water bath shaker. After incubation for various appropriate time intervals, a test tube was removed from the shaker, 900 μL of acetonitrile was added, and the sample was vigorously vortexed for 3 minutes. The resulting solutions were analyzed by analytical HPLC to generate hydrolysis rate data (see table and graphs, below).

5.10 *In Vitro* Prodrug Hydrolysis of Acetate (Compound 4)

To nine 13 mm x 100 mm test tubes was added 5.15 μL each of an 8.741×10^{-4} M aqueous solution of acetate prodrug (Compound 4). To each tube was then added 295 μL of freshly obtained heparinized rat plasma from an adult male Sprague Dawley rat (CD) (source Charles River; Raleigh, NC). The tubes were capped and incubated at 37°C in a reciprocal water bath shaker. After incubation for various time intervals, a test tube was removed from the shaker, 900 μL of acetonitrile was added, the sample was vigorously vortexed for 3 minutes and then cooled to -12°C for between 30 and 90 minutes. The samples were centrifuged at 25°C for 10 minutes at 1,600 g and the resulting clear colorless supernatant solution was analyzed by analytical HPLC (see Figure 2).

THE CLAIMS

We claim:

1. A taxane prodrug comprising:

   (a) at least one taxane; and

   (b) one or more PEG polymers and/or oligomers, each joined to a bonding site on the therapeutic compound by a hydrolyzable bond, said PEG polymers and/or oligomers each:

      (i) comprising a straight or branched PEG segment consisting of 2 to 25 polyethylene glycol units; and

      (ii) optionally comprising a salt-forming moiety.

2. The taxane prodrug of claim 1 wherein the one or more polyethylene glycol oligomer(s) each consists essentially of from 2 to 20 polyethylene glycol units.

3. The taxane prodrug of claim 1 wherein the one or more polyethylene glycol oligomer(s) each consists essentially of from 2 to 15 polyethylene glycol units.

4. The taxane prodrug of claim 1 wherein the one or more polyethylene glycol oligomer(s) each consists essentially of from 2 to 10 polyethylene glycol units.

5. The taxane prodrug of claim 1 wherein the polyethylene glycol oligomer has a number of polyethylene glycol units selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, and 9.

6. The taxane prodrug of claim 1 wherein at least one of the one or more polyethylene glycol oligomer(s) comprises a salt-forming moiety.

7. The taxane prodrug of claim 6 wherein the salt-forming moiety is selected from the group consisting of: ammonium, hydrogen, sodium, potassium, lithium, calcium, carboxylate, chloride, bromide, iodide, phosphate, sulfate and mesylate.

8. The taxane prodrug of claim 1 wherein the taxane comprises paclitaxel.

9. The taxane prodrug of claim 1 wherein the taxane comprises a paclitaxel analog which retains some or all of the therapeutic activity of paclitaxel.

10. The taxane prodrug of claim 1 wherein the taxane comprises docetaxel.

11. The taxane prodrug of claim 1 wherein the taxane is derivatized by 1, 2, 3 or 4 of the polyethylene glycol oligomers.

12. The taxane prodrug of claim 1 which, when delivered via the oral route of administration, provides a therapeutically effective dose of the taxane to the blood.

13. A pharmaceutical composition comprising:

(a) a taxane prodrug of claim 1; and

(b) a pharmaceutically acceptable carrier.

14. The pharmaceutical composition of claim 13 in a form suitable for oral administration.

15. The pharmaceutical composition of claim 13 in a form selected from the group consisting of: tablets, capsules, caplets, gelcaps, pills, liquid solutions, suspensions or elixirs, powders, lozenges, micronized particles and osmotic delivery systems.

16. A taxane prodrug comprising a taxane joined by hydrolyzable bond(s) to one or more polyethylene glycol oligomer(s) selected from the group consisting of:

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n-\overset{\overset{\displaystyle R}{|}}{N}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 2)}$$

wherein n is from 1 to 7, m is from 2 to 25, and R is a lower alkyl;

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{H}{N}-(CH_2)_p-\overset{\overset{\displaystyle R}{|}}{N}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 3)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, and R is a lower alkyl;

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{H}{N}-CH_2CH_2(OC_2H_4)_r-\overset{\overset{\displaystyle R}{|}}{N}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 4)}$$

wherein n is from 1 to 6, m and r are each independently from 2 to 25, and R is a lower alkyl;

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2)_p-\overset{R}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mNH_2 \qquad \text{(Formula 5)}$$

wherein n is from 1 to 6, p is from 2 to 8 and m is from 2 to 25 and R is a lower alkyl;

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2)_p-\overset{R}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mNH_3^+X^- \qquad \text{(Formula 6)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, X^- is a negative ion;

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2)_p-\overset{R^1}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mNHR^2 \qquad \text{(Formula 7)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, and R^1 and R^2 are each independently a lower alkyl;

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-CH_2CH_2(OC_2H_4)_mOCH_2-\overset{O}{\overset{\|}{C}}-NH(CH_2)_pN(CH_3)_2 \qquad \text{(Formula 8)}$$

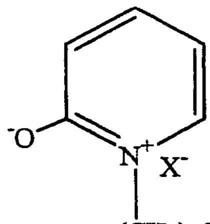
wherein n is from 1 to 6, p is from 2 to 8 and m is from 2 to 25;

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n(OC_2H_4)_mO(CH_2)_p-\overset{O}{\overset{\|}{C}}-O^-X^+ \qquad \text{(Formula 9)}$$

wherein n and p are each independently from 1 to 6, m is from 2 to 25 and X^+ is a positive ion;

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\underset{\underset{R^2}{|}}{\overset{\overset{R^1}{|}}{N}}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 10)}$$

wherein n is from 1 to 5, m is from 2 to 25, and wherein R1 and R2 are each independently lower alkyl; and



$(CH_2)_nCH_2(OCH_2CH_2)_mOCH_3$ (Formula 11)

wherein n is from 1 to 6, m is from 2 to 25 and X^- is a negative ion.

17. The taxane prodrug of claim 16 wherein the polyethylene glycol oligomer comprises a salt-forming moiety.

18. The taxane prodrug of claim 17 wherein the salt-forming moiety is selected from the group consisting of: ammonium, hydrogen, sodium, potassium, lithium, calcium, carboxylate, chloride, bromide, iodide, phosphate, sulfate and mesylate.

19. The taxane prodrug of claim 16 wherein the taxane comprises paclitaxel.

20. The taxane prodrug of claim 16 wherein the taxane comprises paclitaxel analog in which the therapeutic activity of paclitaxel is not completely eliminated.

21. The taxane prodrug of claim 16 wherein the taxane comprises docetaxel.

22. The taxane prodrug of claim 16 wherein the taxane is derivatized by 1, 2, 3 or 4 of the polyethylene glycol oligomers.

23. A pharmaceutical composition comprising:

(a) a taxane prodrug of claim 16; and

(b) a pharmaceutically acceptable carrier.

24. The pharmaceutical composition of claim 23 in a form suitable for oral administration.

25. The pharmaceutical composition of claim 23 in a form selected from the group consisting of: tablets, capsules, caplets, gelcaps, pills, liquid solutions, suspensions or elixirs, powders, lozenges, micronized particles and osmotic delivery systems.

26. The taxane prodrug of claim 16 wherein the taxane is joined by hydrolyzable bond(s) to one or more polyethylene glycol oligomer(s) having the formula:

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n-\overset{\overset{\displaystyle R}{|}}{N}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 2)}$$

wherein n is from 1 to 7, m is from 2 to 25, and R is a lower alkyl.

27. The taxane prodrug of claim 26 wherein the taxane comprises paclitaxel.

28. The taxane prodrug of claim 26 wherein the taxane comprises a paclitaxel analog which retains some or all of the therapeutic activity of paclitaxel.

29. The taxane prodrug of claim 26 wherein the taxane comprises docetaxel.

30. The taxane prodrug of claim 26 wherein the taxane is derivatized by 1, 2, 3 or 4 of the polyethylene glycol oligomers.

31. The taxane prodrug of claim 16 wherein the taxane is joined by hydrolyzable bond(s) to one or more polyethylene glycol oligomer(s) having the formula:

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{H}{N}-(CH_2)_p-\overset{\overset{\displaystyle R}{|}}{N}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 3)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, and R is a lower alkyl.

32. The taxane prodrug of claim 31 wherein the taxane comprises paclitaxel.

33. The taxane prodrug of claim 31 wherein the taxane comprises a paclitaxel analog which retains some or all of the therapeutic activity of paclitaxel.

34. The taxane prodrug of claim 31 wherein the taxane comprises docetaxel.

35. The taxane prodrug of claim 31 wherein the taxane is derivatized by 1, 2, 3 or 4 of the polyethylene glycol oligomers.

36. The taxane prodrug of claim 16 wherein the taxane is joined by hydrolyzable bond(s) to one or more polyethylene glycol oligomer(s) having the formula:

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{H}{N}-CH_2CH_2(OC_2H_4)_r-\overset{\overset{\displaystyle R}{|}}{N}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 4)}$$

wherein n is from 1 to 6, m and r are each independently from 2 to 25, and R is a lower alkyl.

37. The taxane prodrug of claim 36 wherein the taxane comprises paclitaxel.

38. The taxane prodrug of claim 36 wherein the taxane comprises a paclitaxel analog which retains some or all of the therapeutic activity of paclitaxel.

39. The taxane prodrug of claim 36 wherein the taxane comprises docetaxel.

40. The taxane prodrug of claim 36 wherein the taxane is derivatized by 1, 2, 3 or 4 of the polyethylene glycol oligomers.

41. The taxane prodrug of claim 16 wherein the taxane is joined by hydrolyzable bond(s) to one or more polyethylene glycol oligomer(s) having the formula:

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{H}{N}-(CH_2)_p-\overset{\overset{\displaystyle R}{|}}{N}-CH_2CH_2(OC_2H_4)_mNH_2 \qquad \text{(Formula 5)}$$

wherein n is from 1 to 6, p is from 2 to 8 and m is from 2 to 25 and R is a lower alkyl.

42. The taxane prodrug of claim 41 wherein the taxane comprises paclitaxel.

43. The taxane prodrug of claim 41 wherein the taxane comprises a paclitaxel analog which retains some or all of the therapeutic activity of paclitaxel.

44. The taxane prodrug of claim 41 wherein the taxane comprises docetaxel.

45. The taxane prodrug of claim 41 wherein the taxane is derivatized by 1, 2, 3 or 4 of the polyethylene glycol oligomers.

46. The taxane prodrug of claim 16 wherein the taxane is joined by hydrolyzable bond(s) to one or more polyethylene glycol oligomer(s) having the formula:

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{H}{N}-(CH_2)_p-\overset{\overset{\displaystyle R}{|}}{N}-CH_2CH_2(OC_2H_4)_mNH_3^+X^- \qquad \text{(Formula 6)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, X^- is a negative ion.

47. The taxane prodrug of claim 46 wherein the taxane comprises paclitaxel.

48. The taxane prodrug of claim 46 wherein the taxane comprises a paclitaxel analog which retains some or all of the therapeutic activity of paclitaxel.

49. The taxane prodrug of claim 46 wherein the taxane comprises docetaxel.

50. The taxane prodrug of claim 46 wherein the taxane is derivatized by 1, 2, 3 or 4 of the polyethylene glycol oligomers.

51. The taxane prodrug of claim 16 wherein the taxane is joined by hydrolyzable bond(s) to one or more polyethylene glycol oligomer(s) having the formula:

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2)_p-\overset{R^1}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mNHR^2 \quad \text{(Formula 7)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, and R^1 and R^2 are each independently a lower alkyl.

52. The taxane prodrug of claim 51 wherein the taxane comprises paclitaxel.

53. The taxane prodrug of claim 51 wherein the taxane comprises a paclitaxel analog which retains some or all of the therapeutic activity of paclitaxel.

54. The taxane prodrug of claim 51 wherein the taxane comprises docetaxel.

55. The taxane prodrug of claim 51 wherein the taxane is derivatized by 1, 2, 3 or 4 of the polyethylene glycol oligomers.

56. The taxane prodrug of claim 16 wherein the taxane is joined by hydrolyzable bond(s) to one or more polyethylene glycol oligomers(s) having the formula:

$$-\overset{O}{\overset{\|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-\overset{H}{N}-CH_2CH_2(OC_2H_4)_mOCH_2-\overset{O}{\overset{\|}{C}}-NH(CH_2)_pN(CH_3)_2 \quad \text{(Formula 8)}$$

wherein n is from 1 to 6, p is from 2 to 8 and m is from 2 to 25.

57. The taxane prodrug of claim 56 wherein the taxane comprises paclitaxel.

58. The taxane prodrug of claim 56 wherein the taxane comprises a paclitaxel analog which retains some or all of the therapeutic activity of paclitaxel.

59. The taxane prodrug of claim 56 wherein the taxane comprises docetaxel.

60. The taxane prodrug of claim 56 wherein the taxane is derivatized by 1, 2, 3 or 4 of the polyethylene glycol oligomer.

61. The taxane prodrug of claim 16 wherein the taxane is joined by hydrolyzable bond(s) to one or more polyethylene glycol oligomer(s) having the formula:

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n(OC_2H_4)_mO(CH_2)_p-\overset{\overset{\displaystyle O}{\|}}{C}-O^-X^+ \qquad \text{(Formula 9)}$$

wherein n and p are each independently from 1 to 6, m is from 2 to 25 and X^+ is a positive ion.

62. The taxane prodrug of claim 61 wherein the taxane comprises paclitaxel.

63. The taxane prodrug of claim 61 wherein the taxane comprises a paclitaxel analog which retains some or all of the therapeutic activity of paclitaxel.

64. The taxane prodrug of claim 61 wherein the taxane comprises docetaxel.

65. The taxane prodrug of claim 61 wherein the taxane is derivatized by 1, 2, 3 or 4 of the polyethylene glycol oligomer.

66. The taxane prodrug of claim 16 wherein the taxane is joined by hydrolyzable bond(s) to one or more polyethylene glycol oligomer(s) having the formula:

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n-\underset{\underset{\displaystyle R^2}{|}}{\overset{\overset{\displaystyle R^1}{|}}{N}}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 10)}$$

wherein n is from 1 to 5, m is from 2 to 25, and wherein R1 and R2 are each independently lower alkyl.

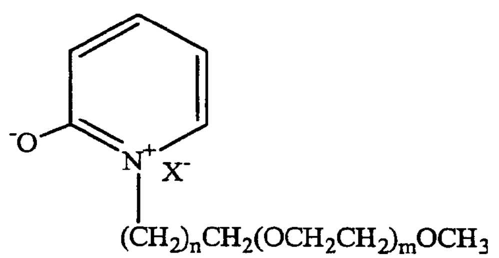
67. The taxane prodrug of claim 66 wherein the taxane comprises paclitaxel.

68. The taxane prodrug of claim 66 wherein the taxane comprises a paclitaxel analog which retains some or all of the therapeutic activity of paclitaxel.

69. The taxane prodrug of claim 66 wherein the taxane comprises docetaxel.

70. The taxane prodrug of claim 66 wherein the taxane is derivatized by 1, 2, 3 or 4 of the polyethylene glycol oligomers.

71. The taxane prodrug of claim 16 wherein the taxane is joined by hydrolyzable bond(s) to one or more polyethylene glycol oligomers(s) having the formula:



(Formula 11)

wherein n is from 1 to 6, m is from 2 to 25 and X^- is a negative ion.

72. The taxane prodrug of claim 71 wherein the taxane comprises paclitaxel.

73. The taxane prodrug of claim 71 wherein the taxane comprises a paclitaxel analog which retains some or all of the therapeutic activity of paclitaxel.

74. The taxane prodrug of claim 71 wherein the taxane comprises docetaxel.

75. The taxane prodrug of claim 71 wherein the taxane is derivatized by 1, 2, 3 or 4 of the polyethylene glycol oligomers.

76. A method of treating a mammalian subject having a taxane-responsive disease condition comprising administering to the subject of an effective disease treating amount of a taxane prodrug comprising:

(a) at least one taxane; and

(b) one or more PEG polymers and/or oligomers, each joined to a bonding site on the therapeutic compound by a hydrolyzable bond, said PEG polymers and/or oligomers each:

(i) comprising a straight or branched PEG segment consisting of 2 to 25 polyethylene glycol units; and

(ii) optionally comprising a salt-forming moiety.

77. The method of claim 76 wherein the one or more polyethylene glycol oligomer(s) each consists essentially of from 2 to 20 polyethylene glycol units.

78. The method of claim 76 wherein the one or more polyethylene glycol oligomer(s) each consists essentially of from 2 to 15 polyethylene glycol units.

79. The method of claim 76 wherein the one or more polyethylene glycol oligomer(s) each consists essentially of from 2 to 10 polyethylene glycol units.

80. The method of claim 76 wherein the polyethylene glycol oligomer has a number of polyethylene glycol units selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, and 9.

81. The method of claim 76 wherein at least one of the one or more polyethylene glycol oligomer(s) comprises a salt-forming moiety.

82. The method of claim 81 wherein the salt-forming moiety is selected from the group consisting of: ammonium, hydrogen, sodium, potassium, lithium, calcium, carboxylate, chloride, bromide, iodide, phosphate, sulfate and mesylate.

83. The method of claim 76 wherein the taxane comprises paclitaxel.

84. The method of claim 76 wherein the taxane comprises a paclitaxel analog which retains some or all of the therapeutic activity of paclitaxel.

85. The method of claim 76 wherein the taxane comprises docetaxel.

86. The method of claim 76 wherein the taxane is derivatized by 1, 2, 3 or 4 of the polyethylene glycol oligomers.

87. The method of claim 76 wherein the taxane prodrug is administered by a route of administration which comprises an oral route of administration.

88. The method of claim 76 wherein the taxane prodrug is administered by a route of administration which comprises a parenteral route of administration.

89. The method of claim 76 wherein the taxane prodrug is administered to the patient by a route of administration comprising a route selected from the group consisting of: intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intraosseous, and intranasal.

90. The method of claim 76 wherein the disease condition is selected from the group consisting of cancers, tumors, malignancies, uncontrolled tissue or cellular proliferation secondary to tissue injury, polycystic kidney disease and malaria.

91. The method of claim 76 wherein the disease condition comprises a cancer.

92. The method of claim 76 wherein the disease condition comprises a cancer selected from the group consisting of hepatocellular carcinoma, liver metastases, cancers of the gastrointestinal tract, pancrease, kidney, colon, cervix, prostate, lung, leukemia and Kaposi's sarcoma. renal, colon, cervix, prostate, and melanoma

93. The method of claim 76 wherein the disease condition comprises ovarian cancer and the taxane prodrug is administered with cisplatin, either simultaneously or sequentially.

94. The method of claim 76 wherein the disease condition comprises breast cancer and the taxane prodrug is administered with doxorubicin, either simultaneously or sequentially.

95. The method of claim 76 wherein the taxane prodrug is administered to the patient by the intraperitoneal route and the disease condition comprises ovarian cancer.

96. The method of claim 76 wherein the taxane prodrug is administered as a component of a pharmaceutical composition comprising:

(a) the taxane prodrug; and

(b) a pharmaceutically acceptable carrier.

97. The method of claim 96 wherein the pharmaceutical composition is in a form suitable for oral administration.

98. The method of claim 96 wherein the pharmaceutical composition is in a form suitable for parenteral administration.

99. The method of claim 96 wherein the pharmaceutical composition is in a form selected from the group consisting of: tablets, capsules, caplets, gelcaps, pills, liquid solutions, suspensions or elixirs, powders, lozenges, micronized particles and osmotic delivery systems.

100. A method of treating a mammalian subject having a taxane-responsive disease condition comprising administering to the subject of an effective disease treating amount of a taxane prodrug comprising a taxane joined by hydrolyzable bond(s) to one or more polyethylene glycol oligomer(s) selected from the group consisting of:

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n-\overset{\overset{\displaystyle R}{|}}{N}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 2)}$$

wherein n is from 1 to 7, m is from 2 to 25, and R is a lower alkyl;

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\displaystyle H}{N}-(CH_2)_p-\overset{\overset{\displaystyle R}{|}}{N}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 3)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, and R is a lower alkyl;

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\displaystyle H}{N}-CH_2CH_2(OC_2H_4)_r-\overset{\overset{\displaystyle R}{|}}{N}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 4)}$$

wherein n is from 1 to 6, m and r are each independently from 2 to 25, and R is a lower alkyl;

$$-\overset{\overset{\displaystyle O}{\|}}{C}-(CH_2)_n-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\displaystyle H}{N}-(CH_2)_p-\overset{\overset{\displaystyle R}{|}}{N}-CH_2CH_2(OC_2H_4)_mNH_2 \qquad \text{(Formula 5)}$$

wherein n is from 1 to 6, p is from 2 to 8 and m is from 2 to 25 and R is a lower alkyl;

$$-\overset{\displaystyle O}{\overset{\|}{C}}-(CH_2)_n-\overset{\displaystyle O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2)_p-\overset{\displaystyle R}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mNH_3^+X^- \qquad \text{(Formula 6)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, X^- is a negative ion;

$$-\overset{\displaystyle O}{\overset{\|}{C}}-(CH_2)_n-\overset{\displaystyle O}{\overset{\|}{C}}-\overset{H}{N}-(CH_2)_p-\overset{\displaystyle R^1}{\overset{|}{N}}-CH_2CH_2(OC_2H_4)_mNHR^2 \qquad \text{(Formula 7)}$$

wherein n is from 1 to 6, p is from 2 to 8, m is from 2 to 25, and R1 and R2 are each independently a lower alkyl;

$$-\overset{\displaystyle O}{\overset{\|}{C}}-(CH_2)_n-\overset{\displaystyle O}{\overset{\|}{C}}-\overset{H}{N}-CH_2CH_2(OC_2H_4)_mOCH_2-\overset{\displaystyle O}{\overset{\|}{C}}-NH(CH_2)_pN(CH_3)_2 \qquad \text{(Formula 8)}$$

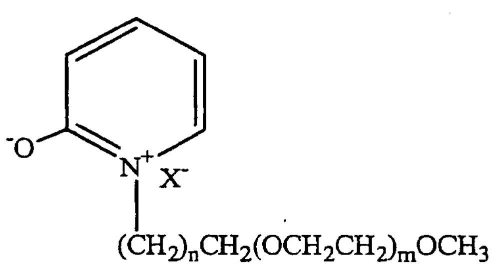
wherein n is from 1 to 6, p is from 2 to 8 and m is from 2 to 25;

$$-\overset{\displaystyle O}{\overset{\|}{C}}-(CH_2)_n(OC_2H_4)_mO(CH_2)_p-\overset{\displaystyle O}{\overset{\|}{C}}-O^-X^+ \qquad \text{(Formula 9)}$$

wherein n and p are each independently from 1 to 6, m is from 2 to 25 and X+ is a positive ion;

$$-\overset{\displaystyle O}{\overset{\|}{C}}-(CH_2)_n-\underset{\displaystyle R^2}{\underset{|}{\overset{\displaystyle R^1}{\overset{|}{N}}}}-CH_2CH_2(OC_2H_4)_mOCH_3 \qquad \text{(Formula 10)}$$

wherein n is from 1 to 5, m is from 2 to 25, and wherein R1 and R2 are each independently lower alkyl;



(Formula 11)

wherein n is from 1 to 6, m is from 2 to 25 and X^- is a negative ion.

101. The method of claim 100 wherein the polyethylene glycol oligomer has a number of polyethylene glycol units selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, and 9.

102. The method of claim 100 wherein wherein the polyethylene glycol oligomer comprises salt-forming moiety selected from the group consisting of ammonium, hydrogen, sodium, potassium, lithium, calcium, carboxylate, chloride, bromide, iodide, phosphate, sulfate and mesylate.

103. The method of claim 100 wherein the taxane comprises paclitaxel.

104. The method of claim 100 wherein the taxane comprises a paclitaxel analog which retains some or all of the therapeutic activity of paclitaxel.

105. The method of claim 100 wherein the taxane comprises docetaxel.

106. The method of claim 100 wherein the taxane is derivatized by 1, 2, 3 or 4 of the polyethylene glycol oligomers.

107. The method of claim 100 wherein the taxane prodrug is delivered by a route of administration which comprises an oral route of administration.

108. The method of claim 100 wherein the taxane prodrug is delivered by a route of administration which comprises an parenteral route of administration.

109. The method of claim 100 wherein the taxane prodrug is administered to the patient by a route selected from the group consisting of: intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intraosseous, and intranasal.

110. The method of claim 100 wherein the disease condition is selected from the group consisting of cancers, tumors, malignancies, uncontrolled tissue or cellular proliferation secondary to tissue injury, polycystic kidney disease and malaria.

111. The method of claim 100 wherein the disease condition comprises a cancer.

112. The method of claim 100 wherein the disease condition comprises a cancer selected from the group consisting of hepatocellular carcinoma, liver metastases, cancers of the gastrointestinal tract, pancrease, kidney, colon, cervix, prostate, lung, leukemia and Kaposi's sarcoma. renal, colon, cervix, prostate, and melanoma

113. The method of claim 100 wherein the disease condition comprises ovarian cancer and the taxane prodrug is administered with cisplatin, either simultaneously or sequentially.

114. The method of claim 100 wherein the disease condition comprises breast cancer and the taxane prodrug is administered with doxorubicin, either simultaneously or sequentially.

115. The method of claim 100 wherein the taxane prodrug is administered to the patient by the intraperitoneal route and the disease condition comprises ovarian cancer.

116. The method of claim 100 wherein the taxane prodrug is administered as a component of a pharmaceutical composition comprising:

(a) the taxane prodrug; and

(b) a pharmaceutically acceptable carrier.

117. The method of claim 116 wherein the pharmaceutical composition is formulated for oral administration.

118. The method of claim 116 wherein the pharmaceutical composition is formulated for parenteral administration.

119. The method of claim 116 wherein the pharmaceutical composition is in a dosage form selected from the group consisting of: tablets, capsules, caplets, gelcaps, pills, liquid solutions, suspensions or elixirs, powders, lozenges, micronized particles and osmotic delivery systems.

Hydrolysis of Acetate Prodrug 4 to Paclitaxel

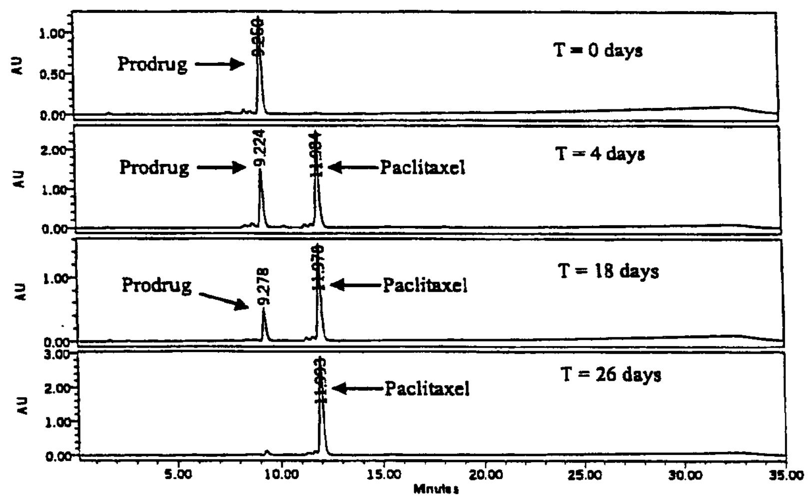


FIGURE 1

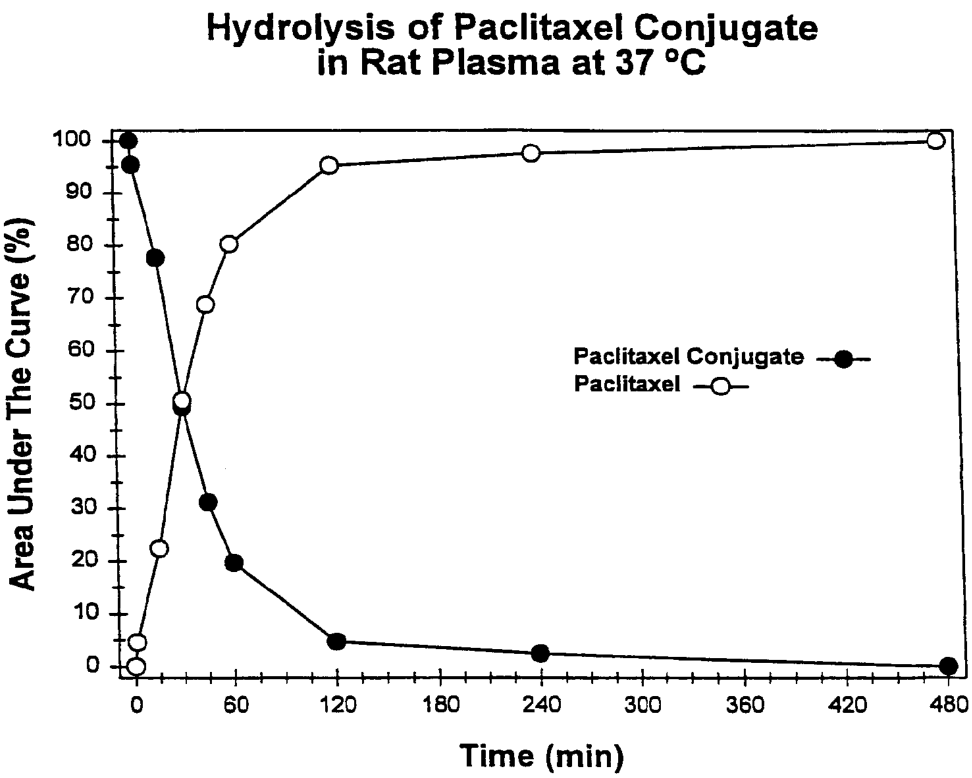

Hydrolysis of Paclitaxel Conjugate
in Rat Plasma at 37 °C
Area Under The Curve (%)
100
90
80
70
60
50
40
30
20
10
0
0
60
120
180
240
300
360
420
480
Time (min)
Paclitaxel Conjugate
Paclitaxel

FIGURE 2